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IDIOPATHIC HYPERCALCAEMIA IN AN INFANT

CLINICAL AND POST-MORTEM FINDINGS IN ONE CASE

BY

I. M. P. DAWSON, W. S. CRAIG and F. J. C. PERERA

From the Departments of Pathology and of Paediatrics and Child Health, the University of Leeds

(RECEIVED FOR PUBLICATION JUNE 11, 1954)

Idiopathic hypercalcaemic syndromes in infancy are now well recognized clinically (Lightwood, 1952a and b; Payne, 1952; Fanconi, Girardet, Schlesinger, Butler and Black, 1952; Creery, 1953; Lightwood and Stapleton, 1953; Lowe, Henderson, Park and McGreal, 1954; Creery and Neill, 1954, and *The Lancet*, leading article July 17, 1954). They are, in our opinion, separate from infantile renal acidosis, and Lightwood and Stapleton divide them into two groups. The classification is accepted by Lowe *et al.* In one group the course is transient and benign. There are no significant bony changes, no cardiac murmurs and probably no hypertension. On recovery the intelligence is normal. In the second group the course is prolonged and severe. There are bony changes resembling osteopetrosis, a loud systolic bruit, hypertension, often hypercholesterolaemia, a characteristic facies and impaired mental development. In the papers mentioned above there is one recorded histological report of a renal biopsy in a case which had run a prolonged and severe course (Lowe *et al.*). In a preliminary communication concerning a similar case (Dawson and Craig, 1954) we had previously tentatively suggested a primary renal origin for the condition. This view has had to be modified as a result of further study. Because necropsy and histological reports on these conditions are rare we think it worth while to present the findings in a single case.

Case Report

Paul D., a boy, was the first child of healthy, unrelated parents. A maternal cousin of the mother had a deformity of the feet. Otherwise there were no known developmental anomalies in the family. Delivery was normal and birth weight 5 lb. 14 oz. Progress in the early months was satisfactory although it was noted that from the age of 3 weeks the baby was unusually quiet, inclined to sleep too much and rather unresponsive to attention. He was first referred to hospital when 23 weeks old on account of anorexia and persistent vomiting for three weeks. On examination the infant was unable to hold his head up. There was generalized hypotonia, gross plagiocephaly and asymmetry of the face and thorax, right calcaneovalgus, a large umbilical hernia, hypertension and a loud systolic murmur audible over the entire chest (Fig. 1). The cardiac murmur had not been present when the baby was thoroughly examined on two occasions during the neonatal period.

FIG. 1.—Paul D., aged 37 weeks. Note the facial and cranial asymmetry.

His weight showed an irregular but progressive decline. Unexplained periods of pyrexia occurred at irregular intervals and the child died unexpectedly during one of them at the age of 47 weeks. Apathy and listlessness, lack of emotional response, reluctance to feed and constipation were constant features in hospital. The abnormal behaviour pattern suggested that mental progress might be impaired. Dogmatic conclusions were not justified, however, in view of the child's age, of the associated physical weakness, and of the fact that impaired hearing was suspected by several independent observers.

The baby was fed wholly at the breast until the age of 3 months when a change was made to a full cream dried cow's milk preparation, and when for the first time concentrated orange juice (1 teaspoonful) and pure cod liver oil (5 drops) were given daily. Medicaments given to the child consisted of six teething powders (each containing $\frac{1}{2}$ grain of calomel) in the sixth month of life; and from the age of 13 to 23 weeks milk of magnesia ($\frac{1}{2}$ teaspoonful) on alternate days, and 2 grains of soda

TABLE 1

BLOOD SERUM BIOCHEMISTRY (mg./100 ml.)

Date	Sodium	Potassium	Total Calcium	Ionized Calcium	Phosphorus	Phosphatase	Chloride	Blood Urea	Urea Nitrogen	CO_2	Cholesterol	Total Protein	Albumin	Globulin	A/G Ratio
17.8.53	300						580			60					
25.8.53			16·0		5·8										
28.8.53			15·7	7·3	6·7	10			26·6		350	6·9			
31.8.53	310	14	16·0		5·0	9	560		27·6		300	6·7	4·5	2·2	2 : 1
12.9.53									54·0						
17.9.53	320	25·5			7·4	17·5		102	47·0		315				
28.9.53			14·1					110	51·0		310				
23.10.53			16·4					88			249	8·5	3·7	4·8	0·8 : 1
28.10.53									50·1						
7.11.53									35·7						
18.11.53									26·5						
2.12.53	345		12·8		5·4	10	540			52	250	7·4			
15.12.53		17·5								55	330	7·1			

TABLE 2

URINARY FINDINGS

Date	Investigation*
31.8.53	Pus cells, numerous, R.B.C.s occasional Predominant growth *Proteus*.
7.9.53	Polymorphonuclear leucocytes, moderate number, some red cells, occasional hyaline casts. *Proteus*. Albumin, trace, *p*H 6·3. Calcium, 12·9 mg. per 100 ml.
24.9.53	Pus cells, moderate number, many cellular casts, granular casts, moderate number. *Proteus*, profuse growth, occasional colony of staphylococcus Albumin, trace, *p*H 7·0
29.9.53	Many polymorphs and some red and epithelial cells Moderate growth of *Proteus*, light growth of staphylococcus, sensitive to chloromycetin Albumin, trace, *p*H 6·3 Calcium 12·8 mg.
16.10.53	Occasional polymorph and red cells. Very occasional granular casts Heavy growth of *Proteus* and a Gram-positive coccus Albumin, trace, *p*H 6·4
10.11.53	Nil Scanty growth of coliform organism of doubtful significance *p*H 6·3, albumin, trace, calcium, 12·9 mg.
17.11.53	Occasional leucocyte and red cell Moderate growth of *Ps. pyocyanea* and a coliform organism
5.12.53	Desquamated epithelial cells and an occasional pus cell Mixed growth *Proteus* and staphylococcus Albumin, trace, *p*H 6·4

* Frequent use was made of Sulkowitch's reagent but on no occasion did the results suggest excessive calcium excretion.

Chromatography established the absence of reducing substances and of any abnormal amino-aciduria.

Urea clearance was 21% (second hour).

TABLE 3

MISCELLANEOUS FINDINGS

Date	Age (weeks)	Investigation	Results and Conclusion
25.9.53	35	Fractional test meal	Acid secretion within normal limits
12.9.53	34	Wassermann	Negative
28.8.53	31	Electrocardiograph	Elevation of ST segment in leads 2, 3, V4 and V6. T waves prominent
12.11.53	42	,, ,,	
		Radiological	
17.7.53	25	Skull and wrist	Fontanelle open Convolutional markings posterior part of skull Three small centres of ossification in wrist
26.8.53	31	Skeleton	No detectable abnormality in bone structure
30.9.53	36	Skull Long bones Abdomen	Bands of increased density at ends of long bones particularly at distal metaphyses of radius and ulna Peripheral density in ossification centres of tarsal bones and at knee joints No evidence of renal calcification
6.11.53	41	Skull Long bone	Skull, basal sclerosis and asymmetry but no abnormality of sutures Long bone, continued deposit of sclerotic bone metaphyses Two ossific nuclei in each wrist. Epiphyses of femoral heads well developed Epiphyses and tarsal bone—central core of bone of normal intensity with existing sclerotic changes situated peripherally Skeletal development not delayed

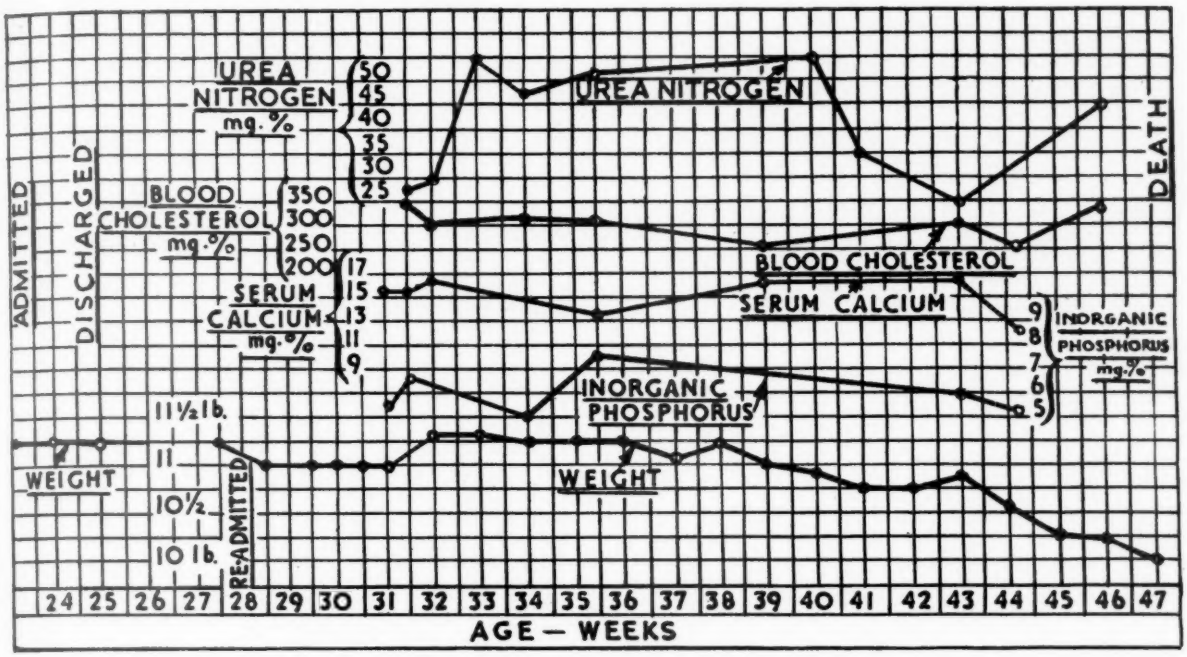

FIG. 2.—Weight trend and changes in blood chemistry related to age.

bicarbonate (in a proprietary mixture) daily. The infant was never given sulphonamides.

INVESTIGATIONS. The results of investigations are detailed in Tables 1-3 and Fig. 2. There were persistently raised serum calcium, blood cholesterol and urea nitrogen levels. Renal function was impaired, but there was no evidence of renal acidosis or of parathyroid hyperactivity. Radiologically there was moderately increased density in certain bones (Fig. 3) but no nephrocalcinosis. Blood cultures at the ages of 27, 44 and 47 weeks were all sterile, and blood counts between July 11 and November 26 gave : Hb 64-79%, R.B.C.s 3·4-4·2 m., W.B.C.s 7,600-20,400 per c.mm. Numerous blood pressure readings were recorded during the last six months of life. Systolic readings were always in the neighbourhood of 140 to 150 mm. Hg and the diastolic readings between 50 and 60 mm. Hg.

The mother of Paul D. has since given birth to a second baby whose progress has been uninterrupted and who at 9 months of age is in every way healthy. The results of examination of the mother's blood one month before delivery of her second baby are summarized in Table 4.

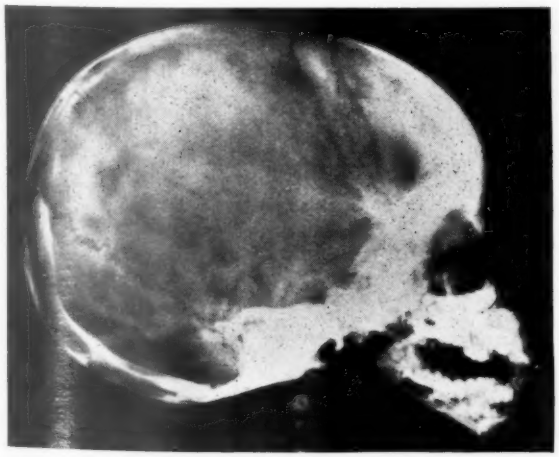

FIG. 3.—Radiograph of the skull at 46 weeks, showing excessive deposit of sclerotic bone at the base of the skull.

TABLE 4

RESULTS OF EXAMINATION OF THE MOTHER'S BLOOD

Serum (mg./100 ml.)	
Calcium	9·1
Inorganic phosphate	3·1
Alkaline phosphatase	12·1
Cholesterol	295
Urea	18
Total protein	5·4
A/G ratio	2·8 : 1

Necropsy

Necropsy was performed 18 hours after death. The body was that of a wasted male child, weight 5·0 kg. (10 lb. 4 oz.) and height 63 cm. (25¼ in.). The upper and lower incisor teeth had erupted. The facial and thoracic asymmetry were not so noticeable as in life.

Cardiovascular System. The heart weighed 55 g. (expected weight 30-40 g.), and there was moderate left ventricular hypertrophy. The remaining chambers and all valves were normal. The foramen ovale and the ductus arteriosus were closed. The coronary arteries and myocardium were normal on section, as was the pericardium. No atheroma or calcification was seen in the aorta.

Respiratory System. There was no infection of the middle ears or tonsils. The trachea and main bronchi were normal. There was patchy bronchopneumonic consolidation of both lower lobes, with moderate congestion of the rest of the lungs, but no evidence of calcification.

Alimentary System. The mouth, pharynx, oesophagus, stomach and small intestine were normal. There were hard, constipated faeces in the transverse, descending and pelvic colon.

The liver (250 g.) was soft and rather pale, and the cut surface suggested fatty change. The gall-bladder was normal, and the bile and cystic ducts were patent. The spleen (16 g.) and pancreas were normal.

Urogenital System. The kidneys together weighed 35 g., and the capsules of both stripped easily leaving a smooth surface. No grittiness was felt on section, and there were no visible calcium deposits. The cortex and medulla both presented a normal appearance. The renal pelves, ureters, bladder, urethra and prostate were normal.

The left testis was in the scrotum and the right testis in the inguinal canal.

Endocrine System. The neck organs were removed en bloc and fixed, and a careful dissection was subsequently made in a search for parathyroid glands. Some 20 small pieces of tissue from this region were sectioned, but only two small pieces of parathyroid tissue were found. No other parathyroid tissue could be identified. The thyroid and suprarenal glands were normal.

Central Nervous System. The brain, spinal cord, and meninges all appeared normal.

Skeletal System. The base of the skull did not appear thickened to the naked eye, and the lower jaw, which was removed, appeared normal. The shaft of the right femur showed definite thickening of the dense cortical bone. No other abnormalities were seen in the other bones examined.

Histology

Material and Methods. Material was taken from the heart, aorta, tonsil, lung, stomach, intestine, liver, pancreas, spleen, kidney, testis, suprarenal, thyroid, parathyroid, thymus, pituitary, brain, spinal cord, upper and lower jaw, base of skull, femur, ribs and voluntary muscle. It was fixed in 10% formol saline. Blocks of kidney were also fixed in cold acetone and embedded in low melting point wax for phosphatase estimations. Bone was decalcified in 20% formic acid.

Haematoxylin and eosin were used for routine staining, and in addition alizarin red, purpurin and xanthopurpurin stains, Von Kossa's method, and the gallamine method of Stock (1949) for calcium; ferri- and ferro-cyanide methods for iron; the azo-dye coupling method of Pearse (1953) using the salt of 4 chloro-o-dianisidine for alkaline phosphatase; and the periodic-acid-Schiff stain, picro Mallory stain, and elastin stain of Weigert for general renal pathology. Sudan IV and Sudan black B were used as fat stains on frozen sections.

The thyroid gland was serially blocked in a further unsuccessful search for parathyroid tissue.

Kidney. Glomeruli are present in normal numbers, and about 90% are normal histologically. In the remaining 10% the principal abnormality is the deposition of hyaline material in glomerular tufts, in some situations diffusely throughout the tuft, and in others localized to one or more lobules (Fig. 4). Certain tufts have been almost completely replaced by hyaline material. Although some hyaline change may normally be seen in kidneys at this age, these findings were considered to be excessive. Occasional epithelial crescents derived from the parietal layer of Bowman's capsule are present (Fig. 5). There is no glomerular calcification.

While some convoluted tubules are normal, others show severe changes, and it is not always possible to differentiate proximal from distal tubules. Vacuolation of proximal tubule cells results in partial or complete occlusion of the lumen in places (Fig. 6). The vacuoles failed to stain with fat stains, with the periodic-acid-Schiff (P.A.S.) method, or with any of the methods for calcium. The distal and collecting tubules contain eosinophilic hyaline casts, which stain red with P.A.S., and basophilic material, which stains positively with the gallamine stain for calcium (Fig. 7) but does not give a positive stain for iron. In certain situations the epithelium of the tubules is destroyed, while in others a layer of regenerating epithelium extends over the hyaline casts (Fig. 8). Calcified material has been extruded into the interstitial tissues of the cortex from the distal tubules (Figs. 9 and 10). A fibrous reaction has been stimulated in these situations, and in the medullary (but not in the cortical) tissues is associated with occasional giant cells. There are no chronic inflammatory cells. The loops of Henle are compressed by a moderate interstitial fibrosis, but are not otherwise greatly altered. A few small collections of lymphocytes are found beneath the renal capsule. There are no inflammatory changes in the renal pelvis. Renal arteries and arterioles are normal. Sections stained for alkaline phosphatase show no constant relationship between sites of phosphatase activity and calcium deposition.

The calcified material in the tubules stains best with gallamine; staining with von Kossa's method is inconstant, and stains for iron are also negative. On the other hand material which has been deposited in the interstitial tissues of cortex or medulla stains readily with

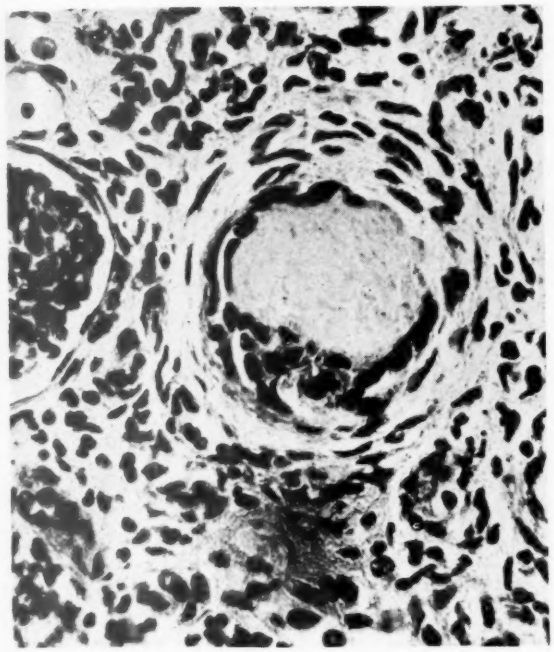

FIG. 4.—Glomerulus showing a moderate degree of hyaline change. (Haematoxylin and eosin. × 380.)

FIG. 5.—Glomerulus showing epithelial crescent. (Haematoxylin and eosin. × 500.)

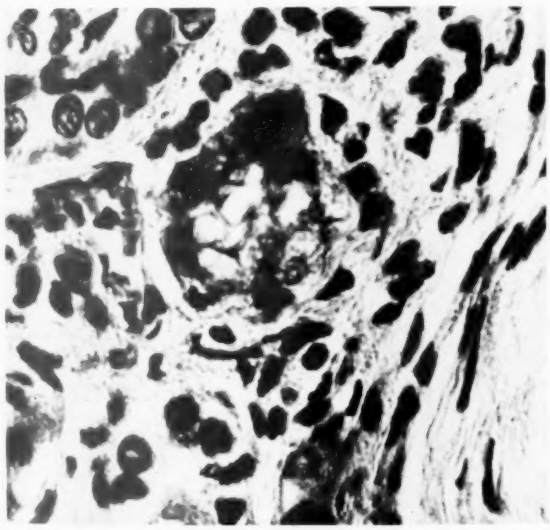

FIG. 6.—Proximal convoluted tubule showing vacuolation of the tubular cells. (Haematoxylin and eosin. × 500.)

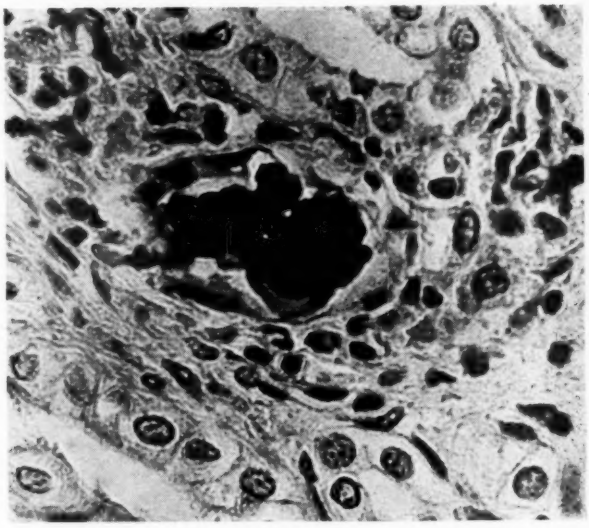

FIG. 7.—Collecting tubule showing calcium deposit in lumen of tubule. (Stock's gallamine method. × 500.)

gallamine and with ferri- and ferro-cyanide methods for iron (Fig. 11). At no time could any positive staining be obtained with purpurin, xanthopurpurin or alizarin red (Cameron, 1930).

Lungs. There is an organizing pneumonic process around fat droplets, which are almost certainly inhaled milk. There is no calcification present in any of the sections examined.

Skeletal Tissues. Femoral and tibial epiphyses and costal cartilages are normal. The shaft of the femur shows a moderate increase in bony thickness when compared with an infant of the same age group, but the

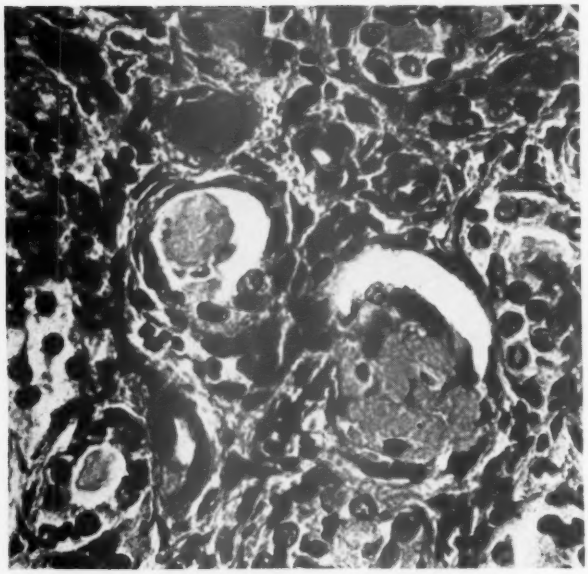

FIG. 8.—Distal convoluted tubule showing re-epithelization of hyaline cast. (Haematoxylin and eosin. × 500.)

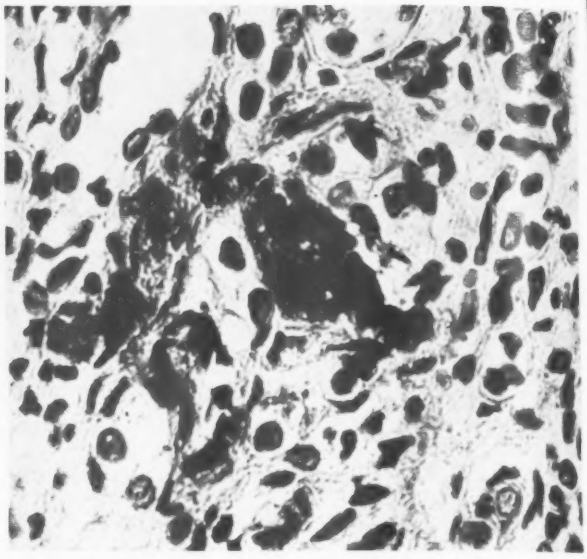

FIG. 9.—Collecting tubule showing calcium deposit becoming extruded from lumen. (Stock's gallamine method. × 500.)

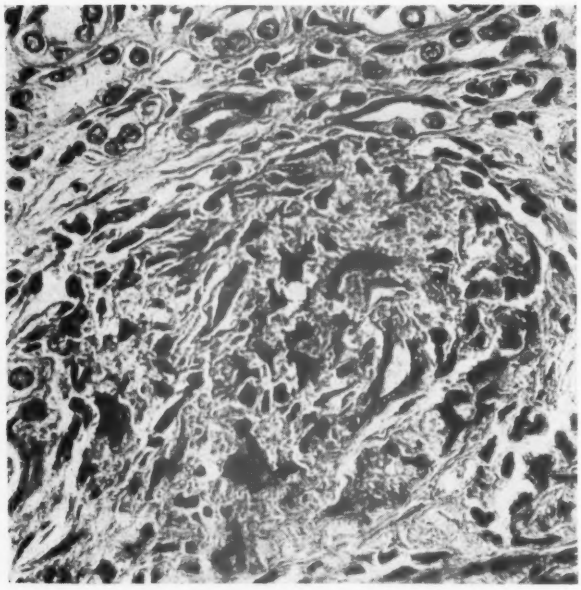

FIG. 10.—Medulla showing calcium deposits with fibrous tissue reaction in interstitial tissue. (Haematoxylin and eosin. × 380.)

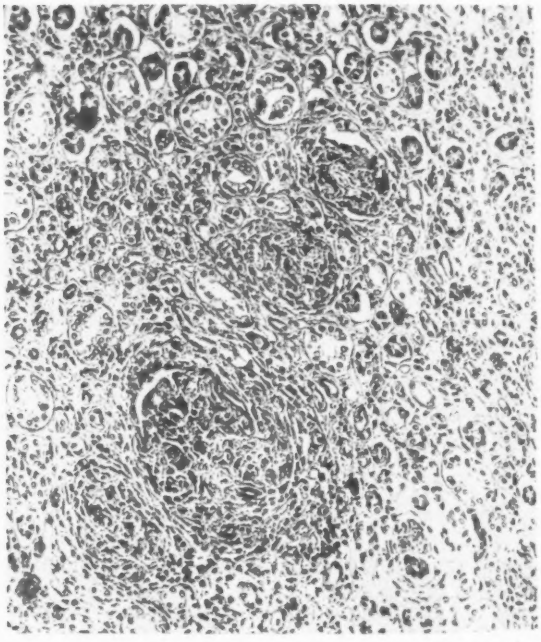

FIG. 11.—A general view of the medulla to show diffuse deposits of calcium with fibrosis. (Haematoxylin and eosin. × 60.)

bone structure is normal. Sections from the base of the skull suggest some thickening but again show normal bone structure.

Sections of the jaws and teeth show normal development and normal calcification of deciduous molars. An unusual and abnormal feature is calcified areas in the pulp of the lower central incisors (Figs. 12 and 13).

Endocrine Glands. The two small pieces of parathyroid tissue show a completely normal structure. The pituitary has not been serially sectioned but there is no indication of a disturbance in the customary ratio of chromophil to chromophobe or acidophil to basophil cells in the sections examined.

The remaining tissues examined are normal. There

is no evidence in the stomach or elsewhere of metastatic calcification.

FIG. 12.—Radiograph of the lower jaw showing calcium deposits in pulp of the incisor teeth.

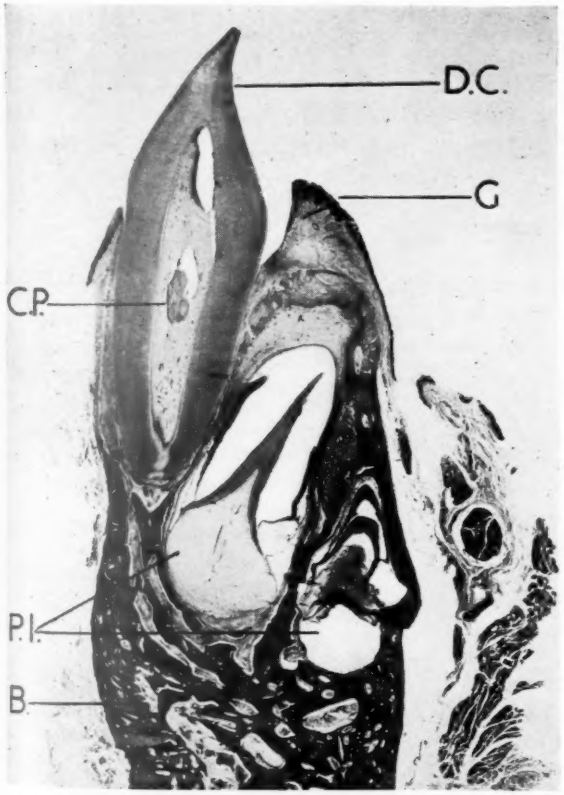

FIG. 13.—Section of an incisor tooth showing permanent incisors (P.I.), gum margin (G.), and abnormal calcium deposit (C.P.) in the pulp of deciduous incisor. (Haematoxylin and eosin. × 6.)

Discussion

Butler, Wilson and Farber (1936) described renal lesions in children with hypercalcaemia and acidosis. They saw calcium deposits between the basement membrane and epithelial cells of collecting tubules, a few deposits in proximal tubules, degeneration of tubular epithelium and calcified deposits surrounded by fibrosis and giant cell infiltration around affected tubules. Their cases appear to belong clinically to the renal acidosis group or possibly to the transient and benign group of idiopathic hypercalcaemia which may sometimes show acidosis. Govan (1950) described hyalinized glomeruli, vacuolation of proximal tubular epithelium, calcified casts in distal and collecting tubules, and deposits of calcium associated with fibrosis in the surrounding tissues in a case of renal acidosis in a girl of 29; death may have been complicated by sensitivity to sulphonamides. The histology of both of these cases is not dissimilar to our own, though there are no calcium deposits between basement membranes and epithelium in our case. Govan attributed the vacuolation of proximal tubules to possible phosphorus absorption, and we were at first inclined to think of the tubular vacuolation in our case as primary, representing a nephron nephrosis of the type seen in sulphonamide or mercury poisoning. The fact that Albright, Consolazio, Coombs, Sulkowitch and Talbott (1940) and Albright, Burnett, Parson, Reifenstein and Roos (1946) postulated a primary tubule defect in infantile renal acidosis, often associated with hypercalcaemia, seemed to support this possibility. Further study has changed this view.

Large amounts of calcium-containing material in distal and collecting tubules justifies acceptance of the view that calcium precipitates out as the filtrate becomes concentrated, and that the interstitial fibrosis and probably the tubular epithelial degeneration are secondary to the extrusion of calcium into surrounding tissues. The positive staining for iron as well as calcium in extratubular but not intratubular material supports this view (Cameron, 1952). Vacuolation of proximal tubules need not be primary, but occurs under appropriate osmotic conditions (Allen, 1951) which may well obtain here. Hyaline glomerular changes, besides occurring normally in infancy, have been described as secondary to hypercalcaemia (Dent, Flynn and Nabarro, 1953). In the case of Paul D. no cause for a primary nephron nephrosis was found. On balance it is considered that the renal changes are to be regarded as secondary manifestations of hypercalcaemia, a view which would explain the similarity of lesions in renal acidosis and a severe and prolonged hypercalcaemia

which are clinically, radiologically and biochemically distinct.

Lowe *et al.* (1954) describe the results of renal biopsy in a child presenting clinical features similar to Paul D. Their findings resemble those in our case in the nature of the cortical and medullary changes, but differ in the presence of a granulomatous reaction around calcium deposits in the medulla as opposed to the cortex and in the presence of many abnormal glomeruli. It cannot be claimed that histological studies have as yet provided conclusive positive evidence concerning the aetiology of idiopathic hypercalcaemia in infancy. Increased alimentary absorption of calcium must be accepted as a possible explanation. If this be the explanation the facts concerning our case lend no support to the view that sensitivity to vitamin D may have been a contributory factor. Excessive intake of alkalis has been suggested as having a bearing on aetiology. The child, the subject of this paper, did receive alkalis in considerable amounts but not until symptoms had already become established. Alkalis may have had an aggravating effect but cannot be regarded as having any aetiological significance. Abnormal histological changes in bone and metastatic calcification were found in a case resembling that of Paul D. in other respects (Baar, 1954). The absence of such findings in the present case cannot be explained.

Summary

A case of idiopathic hypercalcaemia of a severe and prolonged type in a boy was studied clinically and at necropsy.

Clinical and biochemical findings included failure to thrive, lassitude, generalized hypotonia, irregular pyrexia, hypertension with a pronounced cardiac murmur, cranio-facial asymmetry and excessive irregular deposition of bone. Serum calcium, blood cholesterol and blood urea levels were raised, and there was evidence of renal impairment.

Histological findings in the kidneys included deposition of calcium in and around distal and collecting tubules, vacuolation of proximal tubule cells and hyaline glomerular changes. Abnormal histological changes in the bones were not seen. There was no evidence of metastatic calcification. An unexplained feature was calcium deposits in the pulp of certain incisor teeth. The parathyroid glands were normal.

Renal changes are regarded as secondary to hypercalcaemia, which it is suggested may have resulted from excessive absorption of calcium by the alimentary tract.

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THE INVESTIGATION OF A LARGE FAMILY AFFECTED WITH VON WILLEBRAND'S DISEASE

BY

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Originally in 1926 and later in 1931 and 1933 von Willebrand and his colleagues published details of a family with a hereditary haemorrhagic diathesis which has since become established as the clinical syndrome known as von Willebrand's disease (von Willebrand, 1926, 1931; von Willebrand and Jürgens, 1933; Jürgens and Naumann, 1931). Of the 66 members in this family, 22 were affected. The dyscrasia was characterized by a tendency to bleed, especially in the form of recurrent epistaxis and intractable haemorrhage following dental extractions, accompanied by a normal coagulation time, no reduction in the number of platelets, a prolonged bleeding time, and, in the one case so investigated, efficient clot retraction. In this particular family both sexes were affected, the disease being inherited as a Mendelian dominant, but while the disease in females appeared to be either severe or mild in degree, the males were all affected to the same moderate degree. von Willebrand and his colleagues sought to prove that in this condition the platelets were qualitatively deficient. This theory led von Willebrand and his colleagues, and later other authors reporting further similar families, to regard this dyscrasia as being an example of 'thromboasthenia' akin to the condition described by Glanzmann (1918), in which the bleeding tendency was characterized by deficient clot retraction and abnormal platelet morphology.

In 1941 Macfarlane described five cases resembling those of von Willebrand. He demonstrated that there was no platelet abnormality and that clot retraction was normal, but that the capillaries of the nail folds were abnormal in shape and failed to contract after puncture. He suggested that the abnormality was caused by an inherited capillary defect and not by a platelet functional deficiency, pointing out that in the literature of similar cases the clot retraction had usually been reported as normal.

Estren, Sanchez Médal and Dameshek (1946) reviewed 62 cases from the literature and added 11 of their own which they had investigated, adding weight and detail to the clinical picture of the condition but confusion to its aetiology by reverting to von Willebrand's original name of 'pseudo-haemophilia', for, as is pointed out by Biggs and Macfarlane (1953) in their review of the literature, this haemorrhagic diathesis 'bears no genetic, clinical or pathological resemblance to true haemophilia'.

Gradually the clinical features of the syndrome and the haematological findings in it have become clarified until a definite disease entity is now established. Perkins (1946) reported a family of 37 members in which six males were affected in five generations, confirming the general pattern of the condition and adding that it appeared to be cyclic and tended to become less severe with increasing age. The same capillary abnormality noted by Macfarlane was observed, and in this family the disease appeared to be sex-linked. Levy (1947) investigated a family of 62 members extending over four generations and containing 20 affected persons, 12 females and eight males. The onset of the abnormality varied from 4 months to 4 years, and again it appeared to be cyclic and to diminish in severity with the years. One affected member suffered from haematuria for which only the dyscrasia could be found as the cause, and two-thirds of the affected females suffered from menorrhagia and post-partum haemorrhages. Five members had died of haemorrhage—three intrapulmonary, one following a gun-shot wound, and one of uterine origin. Once more the capillary abnormality was reported. These symptoms were again in addition to the accepted pattern of recurrent epistaxis, easy bruising, intractable bleeding following dental extractions, haemorrhage from the gastro-intestinal tract, occasional joint involvement, and the hazard of surgical interference. Revol, Favre-Gilly and Ollagnier (1950) critically reviewed 91 published cases, agreeing that the platelets seemed to be normal in all respects. Lelong and Soulier (1950) again confirmed the

functional normality of the platelets in six cases, and found that the prothrombin consumption test gave normal results, as was confirmed by Cazal and Izarn (1950). The same clinical picture and haematological results have been recorded by O'Brien (1951), reporting a family of 38 members of whom six females and seven males were affected. This author, pointing out that in both hereditary haemorrhagic telangiectasia and von Willebrand's disease the same capillary defect exists, and that the two diseases are inherited in a similar way and may occur in the same family, has suggested the name diffuse capillary telangiectasia for the condition.

From the mass of literature available the clinical picture of von Willebrand's disease becomes clear. The tendency to bleed appears most often in childhood and takes the form of recurrent epistaxis, bruising, bleeding following dental operations, gastro-intestinal bleeding, prolonged bleeding from injury and from operation sites. Menorrhagia and post-partum haemorrhage may be severe in women. Haemarthrosis has been reported, and, rarely, haemorrhage into deep tissues and organs. The sexes are equally affected and the family history in the vast majority of families shows the inheritance of the condition to be of the simple dominant type, though some authors have reported families where sex-linkage appears to be present. The disease appears to be cyclic in character, and to decrease in severity with increasing age.

While doubts as to the clinical picture are never marked, the haematological findings are more confused, mainly due, perhaps, to the difficulties of retrospective assessment of findings where such variations in the normal are accepted and where, therefore, different authorities may disagree on the true diagnosis of certain families in whom divergencies from the accepted pattern occur. It is agreed that the findings in von Willebrand's disease are a prolonged bleeding time, a normal platelet count, and a normal coagulation time. There appears to be no functional abnormality of the platelets. The majority of investigators state that prothrombin times and the results of the prothrombin consumption test are normal. Clot retraction is reported as normal in the great majority of cases, Biggs and Macfarlane in their review of the literature giving a figure of 69 of 73 investigations. Capillary morphology and function have been reported as abnormal by several authors, suggesting that the dyscrasia is the result of this abnormality rather than a defect in the coagulation system.

This paper records a further family of 64 members, extending over five generations, of whom 21 are, or were, affected. A total of 33 members have been examined and investigated, and in 11 affected members the haemorrhagic diathesis has been the subject of a full investigation using current technical methods.

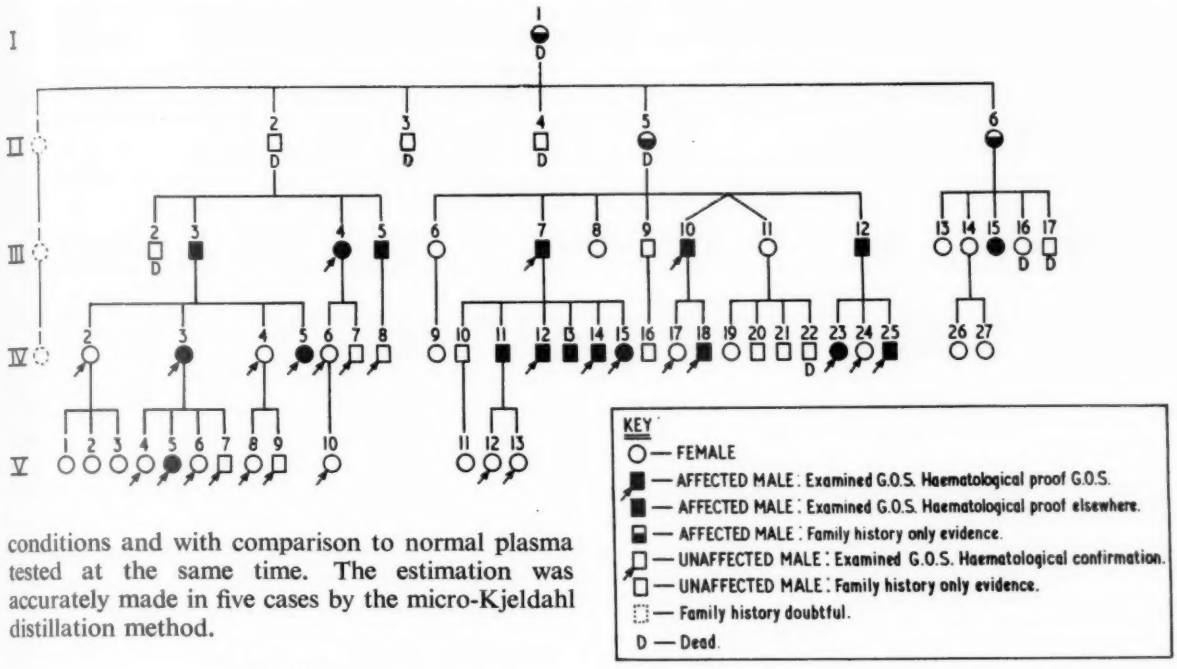
Material and Methods

Interest in the family arose with the examination of one member (IV, 23) attending the hospital as an out-patient with a history highly suggestive of von Willebrand's disease. From this case 64 members of her family have been traced and the history of 33 of them has been taken personally, including 18 of the 21 affected members. In the remaining 31 members the history has been checked from three independent sources before being accepted. Only three affected members have been so assessed, two being dead (I, 1 and II, 5) and one being unavailable for personal investigation (II, 6). The 33 members seen personally were fully examined clinically. In the 18 affected members so examined no organic cause for the bleeding from any individual site was found.

The bleeding and clotting times have been done on at least two occasions on the 15 members seen in whom no history of abnormal bleeding exists. In every case on each occasion the results lay well within the normal limits. The remaining 18 members seen by us have all been affected: in seven of them the bleeding and clotting times have been estimated on several occasions while in the remaining 11, in addition to estimating bleeding and clotting times on several occasions, a full investigation has been made, in seven on two occasions. This has included the following tests:—

Investigation	Method	Accepted Normal
Bleeding time	Duke (1915)	2 to 5 minutes
Clotting time	Dale and Laidlaw (1911-12)	1½ to 3 minutes
Clotting time	Lee and White (1913)	5 to 10 minutes
Platelet count	Cramer and Bannerman (1929)	250,000-500,000 per c.mm.
Clot retraction	Macfarlane (1939)	48-64% serum
Thromboplastin time	Biggs and Macfarlane (1953)	—
Prothrombin consumption test	Biggs and Macfarlane (1953)	Less than 40%
Thrombin generation test	Macfarlane and Biggs (1953)	—
Thromboplastin generation test	Biggs and Douglas (1953)	—

With the exceptions of the methods used for the bleeding time and the platelet count, these being standard in this hospital for many years, all the techniques used are those recommended by Biggs and Macfarlane, and great care has been taken to assure a standard technique. The fibrinogen content of the plasma has been estimated crudely by the addition of thrombin solution under standard


KEY
FEMALE
AFFECTED MALE: Examined G.O.S. Haematological proof G.O.S.
AFFECTED MALE: Examined G.O.S. Haematological proof elsewhere.
AFFECTED MALE: Family history only evidence.
UNAFFECTED MALE: Examined G.O.S. Haematological confirmation.
UNAFFECTED MALE: Family history only evidence.
Family history doubtful.
D — Dead.

conditions and with comparison to normal plasma tested at the same time. The estimation was accurately made in five cases by the micro-Kjeldahl distillation method.

Results

Fig. 1 shows the family tree. Of the total of 64, 38 are female of whom 10 are, or were, affected (two being dead), and 26 are male of whom 11 are affected. The seeming preponderance of males affected is well within the bounds of chance distribution and both sexes in this family are therefore equally affected. From Fig. 1 the disease appears to be inherited as a simple dominant, for there is only the evidence of his family that Case II, 2 was not affected though three of his four children had the condition transmitted to them. In view of the fact that the dyscrasia may be so mild in character in any one person, hearsay evidence, no matter how substantial, must be regarded as inconclusive. This point was borne out in Case III, 10. Two of his brothers, themselves affected, affirmed that he was unaffected, yet at a personal interview later he gave a history of recurrent epistaxis and haemorrhage following dental extractions, 'though nothing like as bad as my brothers', and his bleeding time on two occasions was found to be 10 minutes and in excess of 20 minutes.

Of the 21 affected members there is haematological confirmation in 18, two being dead and one unavailable for investigation and never investigated elsewhere, though there is no doubt clinically that she is moderately affected. The age of onset of the symptoms has been variable: nine members were 5 years of age or less when the disease first became manifest, four were between 6 and 10 years, two were in their 'teens, two showed the first evidence at 21 and 23 years respectively, in two (both dead) the age of onset is unknown, while in the remaining two, in whom abnormal bruising is the only symptom, the onset is difficult to determine but was certainly at a very early age. Of the 43 unaffected members 16 are still under 10 years of age.

The pattern of the bleeding is remarkably uniform and conforms in every way to the classical picture. Of the 21 affected members, 16 have recurrent epistaxis as the main symptom; 11 suffer from prolonged and uncontrollable bleeding following some dental extractions; seven bruise abnormally easily; three have had recurring gastro-intestinal haemorrhages, of whom two have the proven concomitant of peptic ulceration and the third has a clinical history highly suggestive of such without actual confirmation. Of the seven affected females who have passed the menarche only one complains of menorrhagia and that is doubtful, while five of them have experienced no bleeding complication at parturition in a total of 24 births. One member (V, 5) at 5 years is at the moment free of all symptoms, though on two occasions the bleeding time has been in excess of 10 minutes. In this family there has been no case of haemarthrosis, haematuria, or haemorrhage into any cavity or organ. Nor does any affected member suffer from excessive bleeding from cuts or injuries.

The severity of the bleeding varies considerably in the 21 affected members, from the as yet symptom-

less Case V, 5 to the severely disabled Cases III, 5 and III, 7. The last in his boyhood and adolescence was absent from school for more than half each year through recurrent epistaxis, each attack of which lasted for several days and completely debilitated him for two or three weeks at a time. For the same reason he was unable to hold any stable occupation until the age of 24, his epistaxis being complicated by then by frequent haematemeses and intestinal haemorrhages sufficiently severe to require numerous, and at times quite massive, transfusions. Though the attacks of epistaxis have become less frequent and severe with the years the intestinal haemorrhages have remained, and only in his mid-thirties was there proof of concomitant duodenal ulceration. Even now these haemorrhages absent him from work at least twice yearly, and as yet no surgeon has suggested operation for his relief though his history following dental extractions and the records of his bleeding times make it quite clear that he has periods of remission when presumably operation could be undertaken.

Ten of the 21 affected members are affected to a degree which causes but transient embarrassment, while in six more the bleeding requires only short bed rest. Of the remainder, three have bleeding sufficiently severe to necessitate prolonged rest on occasion, while the only two who have required transfusion have already been referred to. In both transfusion has followed intestinal haemorrhage, and Case III, 5 has a history highly suggestive of peptic ulceration though there is no proof.

Bleeding from the nose is in the vast majority the only symptom causing embarrassment, in most being transient but in Case IV, 23 extremely severe. Her parents state that when very young she stopped bleeding only when she 'had bled herself out', and we ourselves have witnessed a fall of haemoglobin from 13·7 g. to 8·1 g. per 100 ml. in a period of two days. Her attacks fortunately are becoming less frequent; even now at the age of 10, whereas from 4 to 8 years of age they necessitated long absences from school on several occasions each year, they now occur roughly twice each year and are much less severe.

The mechanism of the epistaxis is undoubtedly not due to any abnormal venous plexus of the nasal mucosa. Quite apart from the completely negative physical findings in the recorded cases and in this family, the father and uncle of Case IV, 23 (Cases III, 12 and III, 10) were both amateur boxers while in the Royal Navy, the father very much so. No amount of physical trauma caused nasal bleeding, yet within a few days of a fight their dyscrasia could produce considerable haemorrhage, originally lasting several days in the case of the father.

The character of the bleeding in every case old enough for an individual pattern to have become established is quite definitely periodic but little more than that. Those members suffering from epistaxis have no precipitating factor, while the periods of both bleeding and freedom therefrom are entirely personal and completely unpredictable, varying from a few days of scanty bleeding separated by many months of freedom to severe bleeding extending over several weeks with but short remissions and relatively short periods of freedom. The pattern in any one case, however, is uniform: if severe at the onset, or soon after, the affliction remains severe. There is a definite tendency for the attacks to become less severe and less frequent with advancing years in most of the moderately or severely affected members. In the case of bleeding following dental extractions the periodicity of the condition is most marked. All the affected adults have on occasion had bleeding which has remained uncontrolled for several hours or even several days, while on other occasions no haemorrhage has occurred. Four of the adults, while in the Armed Services and where their condition was well known, state quite definitely that at the latter extractions there has been no prolongation of the bleeding time, while at others followed by bleeding the bleeding time has been found to be prolonged. We know that this is so in three other members of the family. The possibility of surgical interference without post-operative haemorrhage is also made clear in this family by the fact that five affected members have had uncomplicated abdominal operations, one of them on three occasions, while a sixth had her tonsils and adenoids removed without post-operative bleeding. There exists in this family no relationship between sex and incidence, severity, age of onset, or site of bleeding.

From all the laboratory investigations the only abnormal finding has been prolonged bleeding time, varying from 7 minutes 30 seconds to several hours and bearing no relationship to the severity of the disease in any one case. In 12 of the 18 cases in which laboratory data are available the bleeding time has been found to be normal on occasions and prolonged on others, and this fluctuation has been observed personally in four cases. Of the remaining six cases, in three the time has been prolonged on every occasion of examination and in the other three prolonged on the one occasion on which the test was done.

In the 11 cases investigated thoroughly all the other findings have been normal, in four on the one occasion on which the full investigation was made and in the other seven on both occasions when

the blood was so examined. The clot retraction on every occasion was normal, there was no defect of the blood coagulation factors, and no abnormality of the number, morphology or function of the platelets. The thrombin generation, thromboplastin generation, and prothrombin consumption tests were all normal. There was no quantitative or qualitative defect of fibrinogen and the thromboplastin time was also normal. The nail-bed capillaries have been studied in these 11 cases, and in the seven other affected members seen by us. Probably through initial inexperience we have not observed any gross abnormality in the shape of the capillaries not also encountered in the normals examined, but in two cases studied later in the series dilatation of some loops has been observed and in these two the capillaries have failed to retract on puncture. Such evidence as this provides does confirm the finding originally reported by Macfarlane and later confirmed by Perkins (1946), Levy (1947), and O'Brien (1951).

Conclusions

The study of this family confirms the established clinical picture of von Willebrand's disease recorded in the numerous reports of similar families contained in the literature. The disease consists of a tendency to bleed, the tendency being cyclic and decreasing with age. The disease becomes manifest usually at an early age, both sexes are equally affected, and the dyscrasia is inherited as a simple Mendelian dominant.

The danger in surgical operations is obvious, but that such may be performed without untoward complication is theoretically possible in view of the periodic nature of the disease, and in the practical sphere by the almost universal statement of patients that they bleed following some dental extractions and not following others. Though the danger in emergency operations remains, it does appear that surgical interference is possible without capillary haemorrhage whenever the bleeding time of the individual patient is within normal limits and that operations should await such a finding.

Laboratory investigation of the bleeding diathesis shows the only abnormality to be a prolonged bleeding time when the patient is in a 'bleeding phase'. The clotting time is invariably normal, the platelets normal in number and in morphology. Most investigators report that clot retraction is efficient and that prothrombin time and consumption are within normal limits. These findings have all been confirmed by a study of this family and in the 11 cases fully investigated the thrombin and thromboplastin generation tests have also shown the function of the platelets to be normal. A study of the nail-bed capillaries has, in two members of the family, shown the defect of retraction first noted by Macfarlane.

Summary

The literature of von Willebrand's disease is reviewed.

A family of 64 members, extending over five generations, and containing 21 affected members, is recorded. The symptoms are detailed and clinical examination of the family confirms the accepted pattern of the disease and reveals no organic cause for the bleeding from any one site.

Full haematological examination of 11 affected members reveals no abnormality of function of the platelets and confirms that the only pathological finding is a prolongation of the bleeding time during a bleeding phase.

It is suggested that surgical interference should be possible during those phases when the bleeding time of an affected member is normal.

We are indebted to Mr. G. W. Cecil for much technical assistance throughout the investigation.

Addendum

Since the acceptance of this article for publication, Case III, 7 has been successfully operated on for his chronic duodenal ulcer. Operation was postponed until his bleeding time was normal and he was operated on by Mr. J. L. Stephen, consultant surgeon, Paddington General Hospital, London. The operation was a routine ante-colic Polya-Hofmeister gastrectomy. No precautions were taken against haemorrhage apart from meticulous haemostasis of all cut surfaces. The patient's bleeding time remained normal for five days after operation and there were no complications.

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NORMAL RENAL FUNCTION IN THE FIRST TWO DAYS OF LIFE

BY

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Our knowledge about renal function in the first two days of human life is meagre. Most of it is due to Thomson (1944, 1947, 1949), Smith, Yudkin, Young, Minkowski and Cushman (1949) and Hansen and Smith (1953). Dean and McCance (1947) measured the inulin, diodone and creatinine clearances of four children aged 2 days, and other investigators have included one or two children under 3 days old in a series which they were studying for one or more aspects of renal function (Dean and McCance, 1948; Rubin, Bruck and Rapoport, 1949; Vesterdal and Tudvad, 1949) but, except in the case of Ames' (1953) work on the excretion of water, there have never been enough of these children to make much of the findings, and our ideas about the function of the baby's kidney are almost entirely based upon studies which have been made on older age groups (Barnett, 1940; McCance and Young, 1941; Gordon, Harrison and McNamara, 1942; Barnett, Hare, McNamara and Hare, 1948; Dean and McCance, 1949; McCrory, Forman, McNamara and Barnett, 1952). Thomson (1944) gave average figures and the individual scatter for the volumes of the urines of newborn infants, their specific gravities and *p*H, the concentration of chloride (Cl) and urea, and later (1949) added his findings for the urea clearances. He also (1947) studied two children with 'dehydration fever'. He made no comparisons with adults.

In studying renal function, particularly clearances, it is usual to give enough fluid either by mouth or vein to promote a large diuresis. This facilitates the collection of specimens, but it would be an unphysiological thing to do to a baby less than 48 hours old who at that time normally passes through a period of undernutrition and dehydration. It would have destroyed one of the main objects of this investigation, moreover, which was to try to piece together some of the events which normally take place during those two days. The babies were investigated, therefore, under standardized but almost normal conditions and compared with adults who had been subjected to what we know is a similar degree of starvation and hydropenia.

Subjects and Methods

Eighteen full-term baby boys and six healthy young men have been investigated. Twelve of the babies were born *per vias naturales*, all without the aid of forceps; five of these babies were first children, and seven of them second or later children. The other six babies were delivered by caesarian section. Permission to make these investigations was obtained from the mother before birth, and soon after birth the baby was fitted with an apparatus for collecting the urine quantitatively, and nursed in the usual way, except that he was not put to the breast and was given in all about 25 ml. of water, spread out over the two days at what seemed the most appropriate moments. Cord blood was obtained, the serum separated, analysed for creatinine, urea, sodium, chloride, potassium and phosphates, and its total osmolar concentration determined by freezing point. Small samples of blood were taken from the heel at the end of 24 and 48 hours and the concentration of urea determined in the serum. Sometimes enough blood was withdrawn at the forty-eighth hour by vein puncture for the more extensive assays usually carried out on cord blood. Urine was collected as it was passed spontaneously and the samples were analysed separately. Very small samples were occasionally pooled. Since babies may be assumed to empty their bladders at birth any 'carry over' of foetal urine may be neglected, but some of the urine formed in the first 24 hours may not have been passed till the second 24 hours. The infants, however, usually emptied their bladders when the samples of blood were taken. If this did not happen at the end of 24 hours, the analytical results obtained on the next specimen of urine were partitioned between the first 24 hours and the second 24 hours, according to the time over which the

urine had been collecting in the bladder. If the baby did not empty the bladder at the end of 48 hours no change in the treatment was made till he voided spontaneously, or a voiding just before the end of the 48 hours was held to terminate the urine collections, and calculations were made to correct the volume in, say, the fortieth to the forty-sixth hour, to the fortieth to the forty-eighth hour.

Six healthy young men, all sailors, were also studied. During the experiment they lived in a small room with an almost constant, comfortably warm temperature. They had nothing to eat, and only 350 ml. of water a day to drink for a period of three days. Samples of blood were taken without anticoagulant before the experiment began, and at the end of each 24 hours during the test, and the serum was separated. All urines were collected under toluol in 24-hour periods.

Total nitrogen in all the urines was determined by the ordinary micro-Kjeldahl technique and the other physical and chemical methods were the same as those used by McCance and Widdowson (1953). The body water of the infants and adults was calculated as described by McCance and Widdowson (1952).

Results

Table 1 gives the average urine volumes per litre of body water and the average osmolar concentrations of the urines passed by the infants during the first and second 24 hours of their lives and by the young men during the second and third days of their dehydration experiment. The figures for the adults on the first day of deprivation have not been given since the volumes were about twice as large and the osmolar concentrations correspondingly less than they were on the second and third days so that they clearly belonged to a transitional period between a state of full nutrition and hydration and one of established starvation and hydropenia. Ladell (1947) has described similar findings. These signs of a transitional period were not evident just after birth and since no observations were made on the third day of life the results for the first and second days have been given. Since infants have a higher rate of metabolism per kg. of body weight and become dehydrated more rapidly than adults, it is open to argument whether they had not reached by the second 24 hours a state of starvation and hydropenia similar in severity to that reached by the adults on the third day. At any rate their average weight loss in two days was 9·3% of their original body weight compared with a loss of 6·1% in three days for the adults. The volumes of urine passed by the adults per litre of body water were slightly greater than those passed by the babies, but the osmolar concentrations were three times as high (Day 1, $t=15{\cdot}8$ $p=<0{\cdot}001$, Day 2, $t=17{\cdot}5$ $p=<0{\cdot}001$). In making these and other calculations of a similar nature the adult figure used for comparison was the average of days 2 and 3. The U/P ratios for the osmolar concentrations averaged no more than 1·25 and 1·53 for the first and second days of life, while they were 3·96 and 4·12 for the second and third days of the adults' hydropenia. These low U/P ratios for infants as compared with those for adults should be contrasted with the findings for hydrated and overhydrated babies only six to 18 days older (McCance, Naylor and Widdowson, 1954).

Table 2 shows the composition of the urines of the infants compared as in Table 1 with those of the adults subjected to similar degrees of starvation and hydropenia. The figures for urea, sodium, chloride and potassium have been given by expressing the molar concentration of each as a percentage of the total osmolar concentration determined by freezing

TABLE 1

VOLUMES AND TOTAL OSMOLAR CONCENTRATIONS OF URINE PASSED DURING FIRST TWO DAYS OF LIFE COMPARED WITH THOSE OF URINE OF ADULTS SUBJECTED TO SIMILAR STARVATION AND HYDROPENIA

		Babies		Adults	
		Day 1	Day 2	Day 2	Day 3
Volume (ml./l. body water)	Average	11·9	15·6	15·7	17·7
	S.D. ..	5·16	8·75	3·23	4·70
Total osmolar concentration (m. osmols/l.) ..	Average	375	465	1,186*	1,261*
	S.D. ..	91·5	51	96*	245*

* Average of Days 2 and 3 1,223, S.D. 152.

TABLE 2

COMPOSITION OF URINE OF INFANTS DURING FIRST TWO DAYS OF LIFE COMPARED WITH URINE OF ADULTS SUBJECTED TO SIMILAR STARVATION AND HYDROPENIA†

Constituents of Urine		Babies		Adults	
		Day 1	Day 2	Day 2	Day 3
Urea	Average	33·0	41·6	44·8	49·1
	S.D. ..	7·2	10·1	4·9	4·3
Chloride	Average	14·0	7·0	7·3	6·8
	S.D. ..	5·67	3·39	1·64	3·33
Sodium	Average	9·7	5·6	11·8	6·9
	S.D. ..	4·33	3·98	2·04	2·18
Potassium	Average	12·0	10·1	4·3*	4·6*
	S.D. ..	2·81	2·06	0·95*	0·73*
Undetermined ..	Average	31·3	35·7	31·8	32·6
	S.D. ..	11·7	13·8	4·20	5·94

* Average of Days 2 and 3 4·44, S.D. 0·77.
† All figures are expressed as a percentage of the total osmolar concentration.

point, since this facilitates comparison of the two age groups and enables the undetermined fraction to be considered as well. Considering the great differences in osmolar concentration, Table 2 shows that the contributions of the solutes were relatively alike. Urea contributed less to the total in the infants but sodium and chloride similar amounts. The sudden reduction of the quota due to these two ions immediately after birth has been described by McCance and Widdowson (1953). A significantly higher proportion of the total osmolar concentration was due to potassium in the infants' urines than in those of the adults (Day 1, $t=6{\cdot}5$ $p=<0{\cdot}001$; Day 2, $t=6{\cdot}7$ $p=<0{\cdot}001$); the fraction which was undetermined was about the same at the two ages. In the infants' urines the proportion due to urea rose slightly on the second day of life ($t=2{\cdot}87$, $p=0{\cdot}01$-$0{\cdot}001$) whereas the proportion due to potassium fell ($t=2{\cdot}23$, $p=0{\cdot}05$-$0{\cdot}02$).

It follows from the figures given in Table 1 that the amount of osmotically active material excreted by the infants per litre of body fluid per day was less than the amount excreted by the adults. The average figure was 5·6 milliosmols per litre of body water per day for the infants as against 19·9 for the adults. There was, however, a further difference between the two age groups in that the milliosmols excreted by the individual adults ranged only from 15·3 to 23·6 (S.D. 2·62) whereas the values for the babies ranged from 2·35 to 9·7 (S.D. 2·24). These individual differences among the infants were far outside any that could have arisen from incomplete collections. Among the adults the ml. of urine/milliosmol varied from 0·74 to 1·07 with a mean of 0·84 and a S.D. of 0·117. The average for the infants was 2·52 (S.D. 0·484) and the extreme values 1·87 and 3·96. If an adult is short of water it is generally agreed that the volume of the urine depends upon the quantity of osmotically active material claiming excretion per unit of time (Ambard and Papin, 1909; Gamble, 1944; McCance, 1945; Rapoport, Brodsky, West and Mackler, 1949). Fig. 1 shows that the volume of urine excreted by

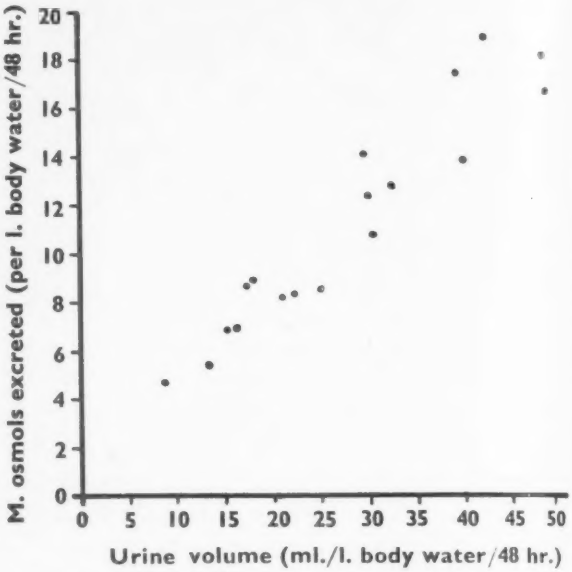

FIG. 1.—The relationship between the excretion of osmolar material and the volume of the urine.

the babies also increased with the output of osmotically active material, Fig. 2 that there was a similar relationship between the volume of the urine and the total nitrogen excreted per day, and Fig. 3 that the urea clearances also rose as the minute volume increased.

It might be surmised from the information already given that the urea and other clearances would be much lower just after birth than among adults who had been correspondingly dehydrated, and that the babies would differ more among themselves. Table 3 shows that this was so. Thomson (1949) found urea clearances of the order of 8 ml./min.

TABLE 3

UREA, SODIUM AND CHLORIDE CLEARANCES OF INFANTS DURING FIRST TWO DAYS OF LIFE COMPARED WITH THOSE OF ADULTS SUBJECTED TO SIMILAR HYDROPENIA AND STARVATION*

		Babies		Adults	
		Day 1	Day 2	Day 2	Day 3
Urea	Average	9·1	14·6	34·4	39·9
	Range	2·7 –19·7	2·4 –32·3	21·7 –48·7	31·5 –52·2
	S.D.	4·39	8·00	8·44	7·42
Sodium	Average	0·089	0·101	0·437	0·300
	Range	0·023–0·347	0·013–0·466	0·305–0·678	0·120–0·442
	S.D.	0·074	0·123	0·133	0·114
Chloride	Average	0·175	0·160	0·384	0·433
	Range	0·032–0·627	0·024–0·450	0·290–0·525	0·229–0·985
	S.D.	0·140	0·142	0·075	0·264

* All figures are expressed as ml./42 l. body water/min.

on the basis of a surface area of 1·73 sq. m. in babies aged 2 to 4 days who were being reared at the breast. This corresponds to 20 ml./min. per 42 litres of body water (McCance and Widdowson, 1952). There is little doubt that the glomerular filtration rates were correspondingly low for, although inulin was never given in order to determine them, the endogenous creatinine clearances were measured in six infants and found to bear the normal and expected relationship to the urea clearances. Averages (ml./42 litres body water/min.) gave for Day 1, creatinine 20·8; urea 8·8, and for day 2, creatinine 25·5; urea 13·9.

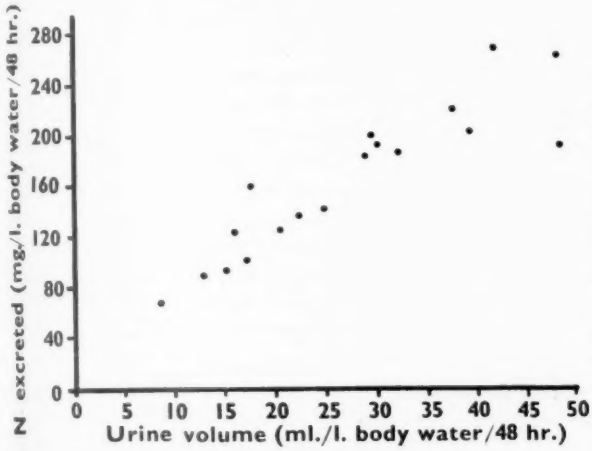

FIG. 2.—The relationship between the excretion of nitrogen and the volume of the urine.

Table 4 shows the total nitrogen, the potassium and the nitrogen : potassium ratios found in the urine of the infants on the first and second days of life and of the adults on the second and third days of dehydration. The infants excreted nearly as much K per kg. of body weight as the adults but only one-third as much N, and consequently their N/K ratios were correspondingly lower than those of the adults. Both differences were highly significant (N excreted on Day 1, $t=16{\cdot}7$ $p=<0{\cdot}001$; Day 2, $t=5{\cdot}65$ $p=<0{\cdot}001$. N/K ratio, Day 1, $t=11{\cdot}9$ $p=<0{\cdot}001$; Day 2, $t=6{\cdot}28$ $p=<0{\cdot}001$). There can be no reasonable doubt about the correctness of these ratios; they agree very well with those given by Smith *et al.* (1949) and by Hansen and Smith (1953) and, as their charts show in two individual babies, the ratios were higher, like the present ones, on the second day than on the first. The difference between the ratios on the first and second days in the present series was a significant one ($t=3{\cdot}45$, $p=0{\cdot}001$).

The phosphate excretions and clearances require

TABLE 4

EXCRETION OF NITROGEN AND POTASSIUM BY INFANTS DURING FIRST TWO DAYS OF LIFE AND BY ADULTS SUBJECTED TO SIMILAR STARVATION AND HYDROPENIA

		Babies		Adults	
		Day 1	Day 2	Day 2	Day 3
Nitrogen* excreted	Average	38·0	77·7	151·0	185·0
	S.D. ..	13·8	35·7	30·2	18·3
Potassium* excreted	Average	13·3	19·9	17·6	22·1
	S.D. ..	5·78	13·1	2·19	4·08
Ratio of N/K in urine	Average	2·9	3·9	8·6	8·4
	S.D. ..	1·00	1·48	1·56	1·27

* Figures for nitrogen and potassium are expressed as mg. per kg. body weight per day.

separate treatment. The inorganic phosphate in cord blood was higher than in the maternal blood and even when infants were given no food there would appear to have been a small rise in the serum P during the first 48 hours of their lives. The increase in eight infants was from an average of 6·0 to one of 8·0 mg./100 ml. The concentration of P in the urines and the amounts excreted per unit of time averaged very much less in the two days after birth than they did in adult life but this statement requires considerable amplification. Before a normal birth the urine may be regarded as containing almost no phosphate (McCance and Widdowson, 1953) and in many babies the amount was found to remain very small for the first 48 hours. In others the excretion of P began to increase soon after birth and was quite considerable by the end of the second day (Fig. 4). These changes in the concentration of P in the urine and in its rate of excretion may have been mediated by the rise in the

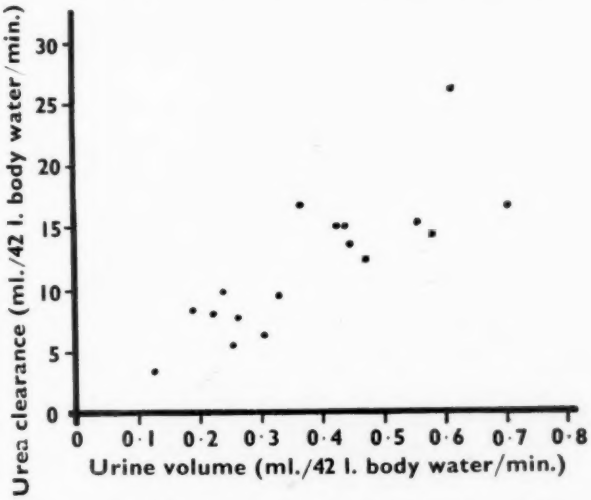

FIG. 3.—The effect of an increase in urine volume on the urea clearance.

serum P but could not be correlated with it or with the excretion of any of the other urinary constituents.

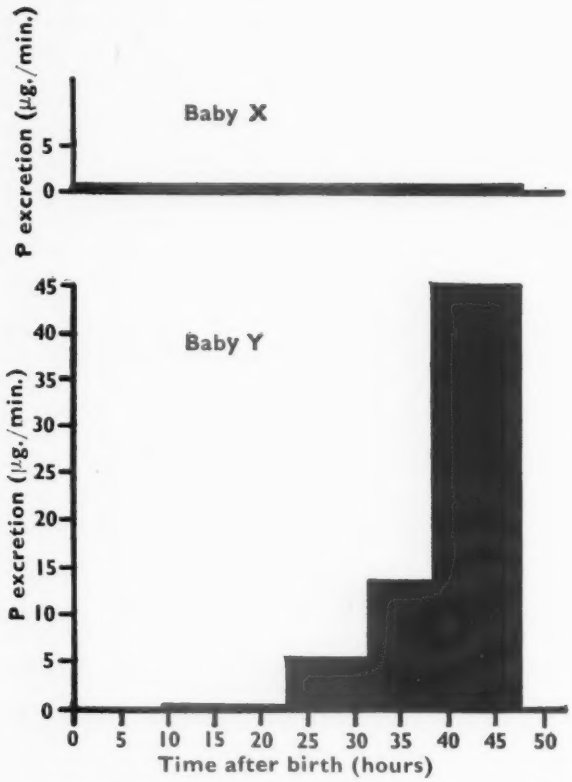

FIG. 4.—Typical examples of the way in which the excretion of phosphorus may behave during the first two days of life.
Baby X Serum inorganic P at birth 4·45 mg./100 ml.
" " " at end of 48 hrs. 7·15 mg./100 ml.
Baby Y Serum inorganic P at birth 6·4 mg./100 ml.
" " " at end of 48 hrs. 7·7 mg./100 ml.

Discussion

The Osmolarity of the Urine. Dubs (1949) considered that the low osmolarity of the urine of dehydrated infants was due to a lack of electrolytes to be excreted. This suggestion runs counter to the work which has been done on osmotic diuresis and the secretion of urine in hydropenic adults, and it seems better at present to regard the volume of the urine in dehydrated infants (as in dehydrated adults) as being fixed by the amount of osmotically active material claiming excretion per unit of time and the concentrating power of the kidney. The latter seems to be relatively constant from one baby to another over the first two days of life whereas the former is extremely variable and the two of them together account for the relationships shown in Figs. 1 and 2. Hansen and Smith (1953) did not recognize this relationship but they gave to eight of their infants 50 ml. and to one 100 ml. of water/kg. of body weight/day and this seems to have hydrated them enough to provide 'free' water for the kidneys to excrete. It did not, however, increase the excretion of nitrogen, sodium or potassium, at any rate in full-term babies. The problem at present seems to be to explain why the osmotically active material claiming excretion per minute should vary as it does from one baby to another whereas in this respect healthy young adults exhibit greater similarity among themselves. It may be the number of nephrons which have become functionally active by the time of birth, or it may be due to the influence of renal haemodynamics upon glomerular function as a whole (McCance and Widdowson, 1954a). There is little evidence at present to indicate whether the difference between one baby and another is due to a different rate of filtration through a similar number of glomeruli or the same rate of filtration through a different number of glomeruli—or even to a little bit of both. The last is perhaps the most probable. It is interesting that the excretion of osmotically active minerals by hydrated as well as by dehydrated infants appears to be higher if they are premature and oedematous than if they are full-term and normal (Smith *et al.*, 1949; Hansen and Smith, 1953) and it is reasonable to submit that in this we may be witnessing the maturation of that function of the kidney which controls the volume of the body fluids.

Partition of Solutes and Nitrogen in Urine. There is little to discuss in the contribution of the various solutes to the total osmolar concentration except the relationships of N and K. In commenting on the N/K ratios, Smith *et al.* (1949) pointed out that Gamble (1947) had noted that dehydration lowered the N/K ratio of adults and implied that this was enough to explain the low ratios found by them in infants. (To be correct, Smith *et al.* worked and wrote in terms of K/N ratios.) This would appear not to be the case because (1) even if dehydration does lower the N/K ratio in adults the ones who were dehydrated for the present investigation had an average N/K ratio of 8·5, still more than twice as high as those of the infants; (2) Hansen and Smith (1953) did not find that hydrating newborn infants sufficiently to increase considerably the volume of the urine altered the N/K ratio found in it. It is evident that the low N/K ratios in infants found in this investigation and by Smith *et al.* (1949) represent a real difference due to age and are not merely the result of dehydration. Apart altogether from the function of the kidney, one explanation is that the

bodies of newborn infants, as of other animals at birth, have a lower N/K ratio in them than those of adults (McCance and Widdowson, 1954b). If the results set out in Table 4 are to be regarded purely from the renal point of view, there are then three questions to be asked and answered. First, Why are the ratios relatively constant in spite of great fluctuations in the total amounts of N and of K excreted from one baby to another and in the same baby from time to time? This is really one aspect of the problem of why the urine should have such a fixed composition and why the excretion of the total milliosmols, nitrogen and urea should be so closely linked with the excretion of water (Table 2 and Figs. 1, 2 and 3). A single mechanism is likely to be responsible for the variations and the only probable one is glomerular filtration (and see above), with which the excretion of both the total N and the K are linked. Second, Why do the ratios rise appreciably on the second day? This is presumably due to the small rise in serum urea and non-protein nitrogen which took place during the first 48 hours of life and led to more nitrogen being excreted with each millilitre of glomerular filtrate. Evidence derived from the study of a few babies suggests that during this time the serum K tended to fall, not to rise. Third, Why are the ratios so much lower than those of adults? Table 5 gives the potassium : urea clearance ratios in the first urine passed after

TABLE 5

AVERAGE RATIO OF POTASSIUM TO UREA CLEARANCES OF INFANTS MEASURED IN FIRST URINE PASSED AFTER BIRTH AND IN FIRST 24 HOURS OF LIFE COMPARED WITH CORRESPONDING RATIO FOR ADULTS SUBJECTED TO SIMILAR STARVATION AND HYDROPENIA

	Average	S.D.
Infants		
First urine passed after birth	0·221	0·113
First 24 hours of life	0·230	0·057
Adults		
Second day of dehydration	0·157	0·055

birth and during the first 24 hours of the infants' lives, and also in the urine of the adults during the second day of dehydration. Urea is not one of the substances which can be used for measuring the glomerular filtration rate, and it forms a somewhat smaller percentage of the total N in the urine of infants than it does in the urine of adults (Barlow and McCance, 1948). Nevertheless, the urea clearance probably bears much the same relationship to the glomerular filtration rate in the hydropenic infants after birth and in the adults (see above for the urea/creatinine clearance ratios and Table 5 of McCance and Widdowson, 1953). The potassium : urea clearance ratios of the infants given in Table 5 are higher than those of the adults. The conclusion may therefore be drawn that the N/K ratios are low because the infants extract less K than the adults from, or excrete more K into, each millilitre of their glomerular filtrates. Why they do so is not yet known but there is evidence that they probably reabsorb more Na and Cl than adults after the first few days of life (McCance, 1950).

Urea Clearances and Glomerular Filtration Rates. The low clearances have been described and they require emphasis because within a week or two of birth hydrated and overhydrated infants have been found under test to have urea clearance and glomerular filtration rates equal to those of adults on the basis of body water (McCance *et al.*, 1954). Some stimulus must initiate this rapid development soon after birth, and operate in other newborn mammals, and it must be particularly effective in those like the rat which have such immature renal function at birth. This problem is under investigation.

The Excretion of Inorganic Phosphate. The excretion of P before and after birth was discussed by McCance and Widdowson (1953), and there seems no need at the moment to withdraw the suggestion made in that paper that the increase in excretion of P after birth was due to an increase of parathyroid activity at that time. It must be admitted, however, that the rise in serum P during the first 48 hours of life may be somewhat against this explanation. The present results on P excretion indicate that if the suggestion was correct the development of these glands took place at a different rate in each baby and that it did not depend, at all events entirely, on the introduction with the food of large amounts of phosphates into the system.

Summary

In the first two days of life, on a limited intake of water and no food, infants (1) excreted volumes of urine which averaged 13·8 ml./l. of body water/day as compared with average volumes excreted by hydropenic and starving adults of 16·7 ml./l. of body water per day; (2) passed urines with an average osmolar concentration of 420 milliosmols/l. as against 1,224 for urines passed by healthy adults; (3) made up the osmolar concentration of their urines in a similar way to adults except that the fraction due to potassium was higher; (4) had a ratio of nitrogen (in mg.)/potassium (in mg.) in the urine which averaged 3·4 (healthy adults similarly dehydrated and starved had a ratio of 8·5); (5) showed a close relation among themselves between the osmotically active material or

the total nitrogen excreted and the volume of the urine; (6) had low urea clearances and glomerular filtration rates. The former averaged 9·1 and 14·6 ml./42 litres of body water/min. on the first and second days whereas those of healthy young adults averaged 37·2 ml./min.; (7) excreted very little phosphate just after birth relative to adults and showed a tendency to increase the rate of excretion by the end of the second day.

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THE INFLUENCE OF EVENTS DURING THE LAST FEW DAYS *IN UTERO* ON TISSUE DESTRUCTION AND RENAL FUNCTION IN THE FIRST TWO DAYS OF INDEPENDENT LIFE

BY

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Since women do not begin to secrete milk freely till the third day after delivery, and no other food is available in nature for the baby, its life is maintained during the first two days after birth largely at the expense of its own tissues, and some destruction of body protein and fat is inevitable. The extent of this protein breakdown was measured by McCance and Strangeways (1954) in six normal full-term babies over the first 48 hours of their lives. During this time the infants were given 25-50 ml. of water but no food, and their basal metabolic rates (B.M.R.) were determined at intervals. The net amount of nitrogen (N) appearing in the form of end-products varied from 49 to 108 and averaged 75 mg./kg./24 hr.; the B.M.R. averaged 50 K Cals/kg./24 hr. The latter is close to the figures obtained by others. In the course of this work one baby was studied (No. 2 in the present series) who had been born after a very difficult labour and who was post-mature. His blood urea level rose to 106 mg./100 ml. and his net catabolism of protein set free 190 mg.N/kg./24 hr. This was considered in all probability to be unphysiological and the baby was excluded from McCance and Strangeways' normal series. It was thought at the time that events during the last few days *in utero* might have been responsible for the high rate of protein breakdown. The matter has now been further investigated and the results form the basis of this paper, but since the B.M.R. of the baby studied by McCance and Strangeways (1954) was perfectly normal (47·5 K Cals/kg./24 hr.), and since such determinations are extremely difficult and laborious, no further work has up to the present been done on them.

Aspects of renal function in premature infants during the first few days of life have been studied by Smith, Yudkin, Young, Minkowski and Cushman (1949), in premature and full-term infants by Hansen and Smith (1953) and in healthy full-term infants also by Thomson (1944, 1949) and McCance and Widdowson (1954a). The studies of McCance and Widdowson were conducted concurrently with the ones now being described, and the findings have provided standards of normality with which to compare the present ones.

Subjects and Methods

Ten full-term or post-mature baby boys who were delivered by the application of forceps have been studied. For this procedure Mother 1 was given a caudal anaesthetic; all the others a general one. The reasons why a forceps delivery was necessary varied from one baby to another as did also the condition of the infants at birth. Table 1 gives some further details of the mothers, all primiparae, of their history, labour and delivery, and of the babies they bore. These facts may be as important as the chemical findings because the two will ultimately require to be correlated more satisfactorily than is possible at present with the limited numbers available. Forceps were applied to baby 9 for maternal prophylaxis, and he and baby 10 appeared little the worse of the operation although the latter's heart rate had caused anxiety before delivery. Babies 4 and 6 were both in a bad state at birth but the latter made a rapid recovery. Babies 1, 2, 3, 5, 6 and 8 had been judged post-mature by the menstrual dates and were delivered after artificial inductions or prolonged and anxious labours. Five of them were post-mature in Clifford's (1953, 1954) sense of the term and all had a very hazardous entry into the world. No. 7 also appeared post-mature and it is probable that the expected date of delivery was wrong. It is impossible, however, to grade the trauma except on general clinical grounds, and there

TABLE 1
CLINICAL NOTES ON MOTHERS AND BABIES

MOTHERS

No.	Age (years)	Pregnancy	Onset of Labour	Duration of Labour (hours)		Delivery Date (days later + earlier − than expected)	Reasons for Forceps Extraction	Drugs
				1st stage	2nd stage			
1	20	Normal	Surgical induction	66	1·0	+19	Prolonged labour and foetal distress	Omnopon gr. $\frac{1}{3}\times2$ Pethidine mg. 100×6
2	26	Normal	Surgical induction	19	3·0	+24	Delayed 2nd stage and foetal distress	Pethidine mg. 100×2
3	37	Normal	Surgical induction	53	—	+14	Prolonged labour and foetal distress	Pethidine mg. 100×5
4	27	Normal	Spontaneous	5 days	1·7	+ 8	Prolonged labour, uterine inertia	Morphia gr. $\frac{1}{4}$ Pethidine mg. 100×6
5	31	Normal	Spontaneous	22	6·5	+16	Prolonged labour and foetal distress	Pethidine mg. 100×2
6	25	Toxaemia	Spontaneous	44	4·5	+17	Prolonged labour, delayed 2nd stage	Pethidine mg. 100×2
7	24	Toxaemia	Surgical and medical induction	5	0·5	− 4	Foetal distress	Pethidine mg. 100×4
8	21	Normal	Spontaneous	48	2·0	+ 9	Prolonged labour and foetal distress	Pethidine mg. 100×5
9	31	Latent T.B., hypertension, oedema of ankles	Spontaneous	4	1·0	− 6	Prophylactic	Pethidine mg. 100×1
10	24	Normal	Spontaneous	9	3·2	− 2	Foetal distress	Omnopon gr. $\frac{1}{2}$ Pethidine mg. 100

BABIES

No.	Body Weight (kg.)		Condition at Birth	Signs of Post-maturity	Skull Moulding	Placenta	Establishment of Respiration	Condition during First 48 Hours
	Birth	48 hrs.						
1	3·0	2·8	Asphyxia	Skin dry and yellow	Severe	Degenerated appearance	30 min.	Atelectasis, signs of cerebral damage
2	3·0	2·9	Cord tightly round neck, asphyxia	Skin dry, body long and thin	Severe	Some infarcts	5 min.	Good
3	3·1	2·9	Limp and shocked	Skin dry and brown	Severe	Granulated and dry	10 min.	Ill, slight atelectasis, signs of cerebral damage
4	3·3	3·0	Cord twice round neck, limp and shocked	None	Very severe	Granulated and dry	3-5 min.	Good
5	3·9	3·7	Asphyxia, slightly anaesthetized	Skin brown, body long and thin	Severe	Granulated and discolored	5-15 min.	Shocked for 24 hours
6	3·2	2·9	Shocked and anaesthetized	None	Severe	Normal	3-5 min.	Good
7	3·4	3·2	Shocked	Skin brown	Very severe	Stained, infarcts	Immediate	Good
8	3·7	3·4	Asphyxia	Skin dry and yellow	Severe Bruised	Granulated and dry	30 min.	Good
9	4·2	3·8	Good	None	Very slight	Normal	Immediate	Good
10	3·7	3·4	Good	None	Moderate	Normal	Immediate	Good

was no common yardstick by which the chemical and physical findings could be compared.

The babies were handled and nursed as described by McCance and Widdowson (1954a) and the physical and chemical methods were the same as those used by McCance and Widdowson (1953). The figure for the net amount of nitrogen appearing in the form of end-products was calculated from the rise or fall in the amount of urea in the body fluids and the total nitrogen excreted. Clinically, all the infants did well and developed normally although some were a cause of considerable worry for a time.

Results

Table 2 gives the volumes and the osmolar concentrations of the urines passed by the babies during the first 48 hours of their lives and also the average results which have been obtained in 18 normal babies delivered without forceps (McCance and Widdowson, 1954a). The volumes passed by the distressed babies were very variable but on the whole they were low and in some cases very low. It is, however, impossible to relate them confidently with any clinical grading, for baby 3 passed a volume well above the normal mean and some of the normal babies had small urine volumes. The total osmolar concentrations of the urine were much the same as those of the normal children although the concentration of urea in the blood was considerably higher

TABLE 2

VOLUMES AND TOTAL OSMOLAR CONCENTRATIONS OF URINE PASSED BY 10 BABIES DELIVERED BY FORCEPS DURING FIRST TWO DAYS OF LIFE COMPARED WITH THOSE OF 'NORMAL' BABIES SUBJECTED TO SIMILAR DEGREES OF STARVATION AND HYDROPENIA

Baby No.	Volume (ml./l. body water) in 48 Hours	Total Osmolar Concentration (m. osmol./l.)
1	13·1	372
2	15·2	484
3	58·2	295
4	20·9	459
5	12·7	471
6	30·5	434
7	4·4	500
8	10·4	408
9	24·7	426
10	37·3	339
Average	22·7	419
Average for 'normal' babies	27·5	420
Range	8·7–48·7	288–536

(see below). This may be a matter of age, for Kerpel-Fronius, Varga, Kun and Vönöczky (1954) always found osmolar concentrations below the normal in the urine of older infants with nitrogen retention due to dehydration.

Table 3 gives the composition of the urines, each constituent being expressed as a percentage of total osmolar concentration and again the average figures for normal babies have been added for comparison. The proportion of the osmolarity due to urea was about normal but the average proportion due to chlorides significantly less for the distressed group ($t=2·82$, $p=0·01$), and, if these babies are considered individually, babies 9 and 10, the two most normal clinically, had perfectly normal percentages whereas babies 7 and 8 had values which were outside the normal range.

These comments about chlorides apply with greater force to potassium ($t=5·04$, $p=<0·001$)

TABLE 3

COMPOSITION* OF THE URINE OF 10 INFANTS DELIVERED BY FORCEPS DURING FIRST TWO DAYS OF LIFE COMPARED WITH THAT OF 'NORMAL' BABIES AND OF ADULTS SUBJECTED TO SIMILAR DEGREES OF STARVATION AND HYDROPENIA

Baby No.	Urea	Chloride	Sodium	Potassium	Undetermined
1	31·4	5·3	9·3	2·2	51·8
2	36·1	4·5	2·2	4·7	52·5
3	46·7	5·1	11·0	7·0	30·2
4	42·5	5·5	5·2	4·4	42·4
5	33·2	6·3	5·0	7·8	47·7
6	42·6	7·4	7·6	8·3	34·1
7	27·3	3·3	4·5	3·8	61·1
8	58·8	2·2	2·9	2·2	33·9
9	28·3	9·7	8·7	8·3	45·0
10	40·6	11·3	9·0	11·5	27·6
Average ..	38·7	6·1	6·5	6·0	42·7
Average for 'normal' babies ..	37·3	10·5	7·4	11·0	33·8
Range ..	22·5–51·7	3·7–20·4	3·2–16·7	6·8–14·3	11·0–54·4
Average for adults ..	47·0	7·0	9·3	4·5	32·2

* All figures are expressed as a percentage of the total osmolar concentration.

but not to sodium, and the departure from the normal percentages for chlorides and potassium makes the percentages for the distressed babies come to lie nearer those of normal adults (McCance and Widdowson, 1954a). The undetermined percentage of the osmolar concentration had a higher average value among the distressed babies than among the normal ones ($t=2·00$, $p=0·05$) and a higher value than among healthy adults. Here again, however, if the distressed babies are split up by the clinical grading, baby 10 had a low proportion of undetermined matter whereas babies 1, 2 and 7 had extremely high ones.

Table 4 shows the concentration of urea in the

TABLE 4

CONCENTRATION OF UREA IN CORD SERUM OF 10 BABIES DELIVERED BY FORCEPS AND AFTER 48 HOURS OF DEHYDRATION AND HYDROPENIA

Baby No.	Concentration of Urea in Serum (mg./100 ml.)	
	Cord	48 Hours
1	27·0	185·0
2	19·2	106·0
3	68·3	103·0
4	39·5	89·0
5	20·7	78·6
6	43·5	82·6
7	36·7	105·0
8	67·4	117·8
9	17·2	51·4
10	23·4	42·0
Average	36·3	96·0
Average for 'normal' babies	22·4	37·2
Range	12·6–41·3	16·8–56·3

serum of each of the distressed babies at birth (cord serum) and at the end of 48 hours, and also the average value and the range for babies delivered without the aid of forceps. There is a hint, which will require confirmation, that the urea concentration in the cord blood of the distressed babies was already higher than in normal babies. There is, however, no doubt that it was much higher at the end of 48 hours. All the figures were above the normal average and all except babies 9 and 10 above the highest normal figure.

TABLE 5

NET AMOUNT OF NITROGEN APPEARING AS END-PRODUCTS, PROPORTION EXCRETED, AND UREA CLEARANCES OF 10 INFANTS DELIVERED BY FORCEPS DURING THE FIRST TWO DAYS OF LIFE COMPARED WITH AVERAGE VALUES FOR 'NORMAL' BABIES AND ADULTS

Baby No.	N Appearing as End-products (mg./kg./body wt./24 hr.)	Percentage of N Excreted	Urea Clearance over 48 Hours (ml./42 l. body water/min.)
1	284	9	1·2
2	190	24	2·7
3	146	66	6·5
4	134	45	5·6
5	128	28	4·1
6	127	56	8·3
7	124	11	0·8
8	108	32	2·1
9	100	49	8·2
10	97	73	12·4
Average	144	39	5·2
Average for 'normal' babies	79	80	11·9
Average for adults	174	96	37·1

Table 5 shows the net amount of N appearing in the form of end-products, the proportion of this excreted and the urea clearances of the babies delivered by forceps compared as before with the normal infants and the adults. All the first named had a protein breakdown above the normal average although babies 8, 9 and 10 were within the normal range. Babies 4, 5, 6 and 7 were well above it. Babies 1, 2 and 3 broke down most protein and baby 1 was outstanding in this respect. The proportion of the nitrogenous end-products which were excreted by these distressed babies averaged considerably less than it did among the normal babies but here again there were differences within the group. Babies 1, 2 and 7, the worst in so many ways, excreted less of their nitrogenous end-products than any of the others; baby 10 excreted nearly as much as the normal average. Baby 3 was interesting in that, although his catabolism was high, his urine volume was also sufficiently high to be well above the normal average and he excreted 66% of the N in the protein he broke down. With urine volumes no greater than the normal, with similar osmolar concentrations and with similar percentages of this due to urea (Tables 2 and 3), it is evident that the rise in the concentration of urea in the body fluids must have meant low urea clearances and the last column in Table 4 shows that this was so. Babies 1, 2, 7 and 8 had the lowest.

Table 6 shows the total N and the potassium (K) excreted by the distressed babies in mg./kg. of body weight/48 hr. It also shows the N/K ratio in the urine and the ratio of the N appearing as end-products to the K excreted. The averages for the normal babies and the adults are also given. The amount of N excreted was not far from the normal. It must be pointed out that this was fortuitous, and was due to a combination of a fall in the urea clearance and a rise in the nitrogenous end-products to be excreted. Some of the babies excreted very little K, particularly babies 1, 7 and 8. Consequently, the N/K ratios in the urine were sometimes very high and the only really normal ones were those of babies 9 and 10. Since these distressed babies all broke down much of their body protein and tended to excrete little K it follows that some of them must have had very abnormal ratios for the mg. N appearing as end-products per K excreted to the mg. Table 5 shows that this was so, and if Tables 4 and 5 are compared it will be noted that there was an inverse relationship between the urea clearance and the urinary N/K ratio, so that the higher urea clearances were associated with low ratios and vice versa.

TABLE 6

TOTAL NITROGEN AND POTASSIUM EXCRETIONS AND N/K RATIOS OF 10 BABIES DELIVERED BY FORCEPS DURING FIRST TWO DAYS OF LIFE COMPARED WITH AVERAGE VALUES FOR 'NORMAL' BABIES AND ADULTS

Baby No.	N in Urine (mg./kg. body wt./ 24 hr.)	K in Urine (mg./kg. body wt./ 24 hr.)	N/K Ratio in Urine	N as End-products K in Urine
1	24·9	1·4	17·8	202·0
2	44·5	5·2	8·6	36·5
3	96·0	14·9	6·5	9·8
4	59·8	5·6	10·7	24·0
5	36·0	6·2	5·8	20·7
6	70·5	13·9	5·1	9·2
7	14·0	1·1	12·7	113·0
8	34·9	1·3	26·8	83·0
9	48·5	11·6	4·2	8·6
10	71·0	19·6	3·6	4·9
Average for 'normal' babies ..	57·9	16·6	3·5	4·8
Average for adults ..	168·0	19·9	8·5	8·8

The excretion of inorganic phosphate (P) was

followed in the distressed babies, but the observations are so far very incomplete. Unfortunately, it was generally impossible to collect any urine which had been formed *in utero*, for nearly all the babies had emptied their bladders during the throes of delivery, but this was achieved in one case and sufficient specimens of urine have been obtained soon after birth to show the trend of events. The urine of baby 2, formed *in utero*, contained a very high and most unusual concentration of inorganic P (74 mg./100 ml.), and Fig. 1 shows the way in which P was excreted by two of the babies whose mothers had had prolonged and difficult labours. The deviation from the normal is brought out most strikingly by comparing Fig. 1 with Fig. 4 in the paper by McCance and Widdowson (1954a). Clearly the events connected with these abnormal births led to the excretion of phosphate. Resuscitation was accompanied in some infants by a fall to a perfectly normal and very low level of phosphate excretion, to be followed by a rise in the excretion rate with the normal maturation of this function.

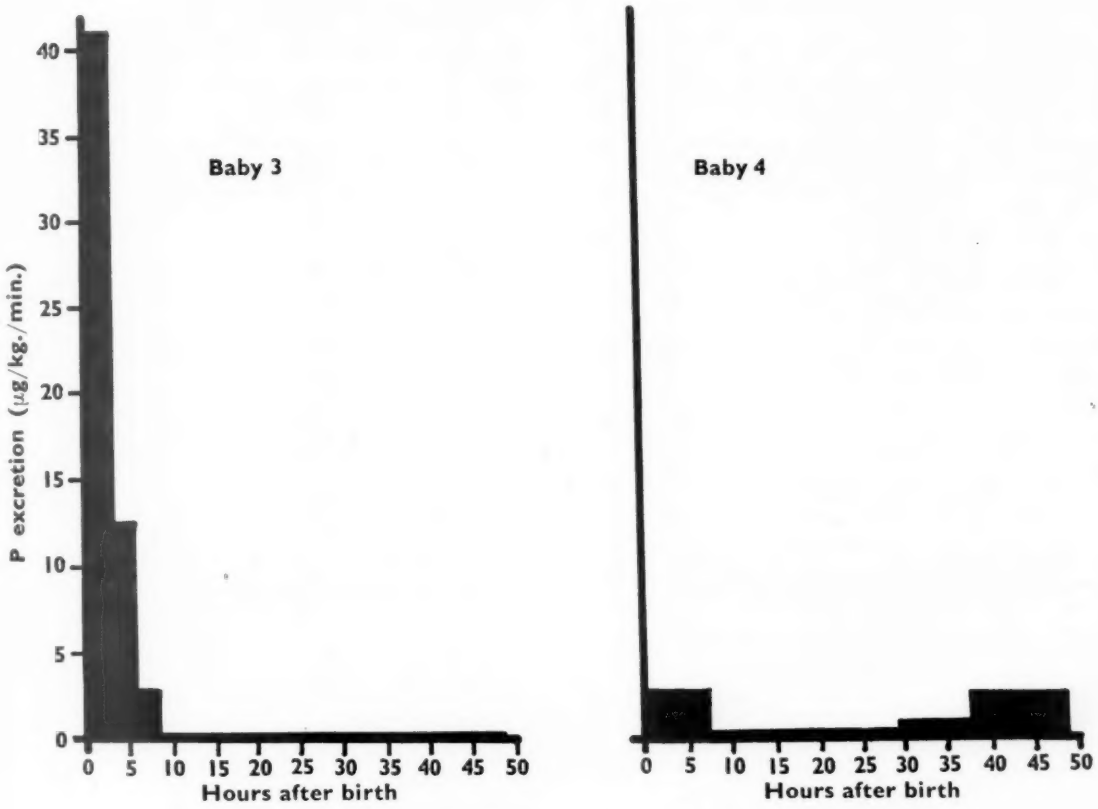

FIG. 1.—Abnormal phosphorus excretions during the first two days of life in babies 3 and 4.

Discussion

The Syndrome. Events connected with a long and difficult labour seem to give rise to a syndrome in the infant which is characterized by (*a*) a relatively large excretion of inorganic phosphate during and immediately after birth, (*b*) an increased destruction of body protein during the first 48 hours of life, (*c*) a low urine volume, a reduced glomerular filtration rate and a poor urea clearance, (*d*) a reduction in the contribution of K and Cl to the total osmolarity of the urine, and certainly no increase in the former commensurate with the increase in the destruction of body protein. This reduction was compensated by an increase in the fraction designated undetermined. The syndrome is undoubtedly characterized by other deviations from the normal which have not yet been described, and, as in so many clinical syndromes, the symptoms and signs may not appear in their entirety in each and every patient.

Previous Observations. Cases of the type presented in this paper have naturally been met with

before but it would appear that the descriptions of them have been incomplete, and the conclusions sometimes incorrect, or misleading. Snelling (1943), for example, in the course of an investigation into tetany of the newborn, described several babies aged 1-4 days who had been born only after prolonged and difficult labours and were found on admission to hospital to have high values for the non-protein nitrogen in the serum. Some of the babies also had high concentrations of inorganic P in their sera. A figure of 8·7 mg./100 ml. was obtained on the first day of life and one of 10·0 mg. on the third. Snelling attributed the abnormal serum findings entirely to a disordered renal function and considered that the low serum calcium and the signs of tetany were secondary to the high serum phosphate. It is probable, however, in the light of the present findings that the most important reason for the high concentration of phosphate and of non-protein nitrogen in the serum was increased tissue destruction during and immediately after birth. Jonsson (1951) published a description of three infants who were in his opinion suffering from lower nephron nephrosis following asphyxia neonatorum. This diagnosis will not explain the urinary findings in babies 1 to 10, for an inability to concentrate the urine and other characteristic features clearly distinguish 'lower nephron nephrosis' (Brun, 1954) from the present syndrome. Jonsson (1951), however, did not consider increased tissue destruction as one of the causes of the high non-protein nitrogen in his cases, although it probably was, and the infants were cyanosed for a long time after birth. By making certain assumptions about the concentration of urea in the blood at birth and allowances for the N in the food and urine, it is possible to get some estimate of the tissue destruction in these babies and the nitrogen liberated was probably over 220 mg./kg./day in two of them and about 150 mg. in the third. Some of Snelling's (1943) babies must have broken down quite as much. Campbell and Dales (1952) described a baby with sclerema neonatorum who was found to have a blood urea of 900 mg./100 ml. on the seventh day of life and histologically normal kidneys after his death on the eighth day. The authors went into the question of how to account for this high figure even with completely functionless kidneys but did not consider abnormal tissue destruction. This may have been the explanation, and a high rate of tissue destruction may be associated with sclerema, whether this is due to a low-grade inflammatory process or to a real deviation of fatty acid metabolism (Harrison, 1926; Harrison and McNee, 1926; Hughes and Hammond, 1948). The baby was said to have had a normal and uncomplicated delivery but it was impossible to get a good account of this.

The Cause: General Features. If we knew why the starving infant catabolized less tissue per basal calorie than an adult (McCance and Strangeways, 1954) it might be easier to discuss the cause of the increased tissue breakdown which seems to be part of the consequence of a really difficult labour. However it is to be interpreted, it would appear from the work of Stoner, Whiteley and Emery (1953) that for the first two days after birth the adrenal cortex is unresponsive to 'stress' and that variations in its hormone output should not be invoked to explain metabolic findings without due consideration. Snelling (1943) suggested that a difficult delivery, slow resuscitation, asphyxia and shock lay behind the abnormalities he observed, and Jonsson (1951) thought that asphyxia leading to 'circulatory' insufficiency with more or less pronounced symptoms of shock was the cause. These suggestions may have truth in them, but they are not the whole truth. Drugs and anaesthetics, the presence—or absence—of known or unknown chemical substances may all operate, and one or other of them underlie the large variations in protein catabolism among 'normal' infants. The high rate of tissue destruction due to a deficiency of vitamin B_{12}, which has been reported in newborn rats (Schultze, 1949; Liener and Schultze, 1950), may probably be excluded, although not as yet by experiment. In this investigation tissue destruction and renal function have been distinguished for the first time and there is reasonable evidence that both may be adversely affected by the traumatic birth but this is not invariable. A high rate of protein catabolism, moreover, has not always been found to be associated with low renal function among the normal infants. The protein catabolism of one normal baby, for example, set free 110 mg. of N/kg. of body weight/24 hr. and this infant had an excellent urine volume and urea clearance, whereas another, who catabolized less protein than any of the other infants except one, had a urea clearance of only 5 ml./42 l./min. Only one normal baby had a lower one.

The Cause: Detailed Considerations. It was pointed out by McCance and Widdowson (1954a) that the excretion of osmolar material, of N and of K was linked with the volume of the urine and that the major variations occurred simultaneously and in the same direction and were probably to be associated with variations in the rate of glomerular filtration. The following comments may serve to throw some light on the findings in the abnormal infants. When the glomerular filtration rate is very low and the

breakdown of tissue protein very high, the concentration of urea and other nitrogenous end-products rises to a considerable height in the serum. A similar rise in K would be incompatible with life and is known, in fact, not to take place. It is suggested, therefore, that (i) the constancy of the composition of the urine in the normal infants was due to the fact that there were only small changes in the composition of the serum, and (ii) the gross rise in the concentration of urea and other nitrogenous end-products in the serum and body fluids of the distressed infants maintained the excretion of N at a relatively normal level in spite of their low glomerular filtration rates and urea clearances, whereas the excretion of K, which was also coupled with the glomerular filtration rate, was low. This will explain the normal output of N in the distressed babies, the small output of K, the high N/K ratios and the fact that the lower the urea clearances and glomerular filtration rates the higher the ratio was found to be. A small rise in the concentration of nitrogenous end-products in the serum is a perfectly normal finding during the first 48 hours of life and probably underlies the rise in the N/K ratio found in the urine of the normal infants between the first and the second day of life (McCance and Widdowson, 1954a). Gamble, Ross and Tisdall (1923) showed that the N/K ratio in the urine of an adult during a prolonged fast with a normal fluid intake was of the order to be expected from the breakdown of cell protoplasm and the excretion of the associated N end-products and salts. This may also be true of infants, for newborn animals have a lower N/K ratio in their cells than adults (McCance and Widdowson, 1954b), but N and K are not necessarily excreted in these ratios after the forced breakdown of much cellular material. McCance and Widdowson (1937), for example, found that when acetylphenylhydrazine was used to hydrolyse the red blood corpuscles in a patient with polycythaemia there was a large rise in the concentration of urea in the plasma and much more of the N than of the K was excreted. The high N/K ratio in the urine to which this gave rise offers a parallel to the findings in the abnormal babies and can be explained in a similar way. A further good example of the way in which the excretion of N can be maintained by a rise in the concentration of urea in the body fluids associated with a fall in the glomerular filtration rate has been provided by Yoshimura, Inoue, Yamamoto, Yamaji, Tanimura, Oohara, Takaoka, Koishi, Funaki and Hayashi (1953). The Buddhist bishop studied by them took no food or drink for eight or nine days. The non-protein nitrogen in the serum went up to six times its initial value but the glomerular filtration rate fell and with it the output of K. The combination of these changes increased the N/K ratio of his urine from about 0·5 to about 7·0. The liver is quite likely to be the site within the body in which the K is retained—at any rate in the first instance (Fenn, 1939; McArdle and Merton, 1952).

Until more is known about the serum values for P in these abnormal infants and their exact glomerular filtration rates, it is impossible to do much to elucidate even the renal element in its excretion much less the metabolic abnormality behind it and this problem must for the moment be left unsolved.

Summary

Following a prolonged and difficult labour, full-term and post-mature infants have been found to show some or all of the following abnormalities:

(*a*) An increased destruction of body protein during the first 48 hours of life; (*b*) a reduced glomerular filtration rate, a poor urea clearance and a low urine volume; (*c*) a high ratio of nitrogen/potassium in the urine; (*d*) a large excretion of inorganic phosphate during and immediately after birth.

All the characteristic features may not be found in each case and the complete 'syndrome' may be due to multiple causes.

In this and the previous investigation we have had a great deal of cooperation and help, both in the wards and in the laboratory. We wish particularly to thank Mr. O. Lloyd, Miss J. E. Bottomley, Dr. D. M. T. Gairdner and the staff of the Maternity Hospital, Cambridge. Miss E. Colbourn, Miss G. Ives, J. W. T. Dickerson and L. A. R. Luff have also given us valuable assistance.

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PROGNOSIS IN IDIOPATHIC THROMBOCYTOPENIC PURPURA OF CHILDHOOD

BY

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Many articles have been written about idiopathic thrombocytopenic purpura but few differentiate adequately between children and adults. This is unfortunate, as it is generally agreed that the disease is much milder in children than in adults, and has a better prognosis. We propose, therefore, to discuss a number of cases in children and to review some other series in order to obtain a clearer picture of the course and prognosis of the disease in children.

Criteria for Inclusion

This series of 43 cases includes all the 40 cases under the age of 15 years seen in three Manchester children's hospitals in the years 1948-53 inclusive. The term 'thrombocytopenic' is used in this study to indicate a platelet count of less than 120,000 per c.mm. determined by direct methods. In all cases except three the platelet count was below 100,000 on more than one occasion. Cases of thrombocytopenia following acute infections have been included, but not those occurring during the course of fulminating infections or other diseases, during the neonatal period, or as a reaction to drugs.

Clinical Findings and Course

The clinical features were typical; most cases had bruising and petechiae and a few had haemorrhages from one or more sites; one case had mild epistaxis as the only clinical manifestation. The spleen was palpable in only 11 cases and the enlargement was but slight. Clement and Diamond (1953) reported well-marked systolic bruits in 8% of their cases, but we have been unable to confirm this observation.

Only one relative of 32 of the surviving children had any tendency to bleed or bruise easily; this was the mother of a child with chronic idiopathic thrombocytopenic purpura. Her platelet count, however, was normal.

The age distribution is shown in Fig. 1; there was no difference in distribution between the sexes. The duration and outcome of the disease are shown in Fig. 2.

Most of the cases fall into one of two groups: an 'acute group' of 24 patients, who either died or recovered spontaneously and completely within six months of the onset, and a 'chronic group' who were ill for more than six months. In addition there were seven 'indeterminate' patients who underwent splenectomy within four months of the onset of symptoms. Three of these indeterminate cases had well-defined onsets, and their symptoms—though not their platelet counts—seemed to be improving at the time of splenectomy; two more were severely ill with a sudden onset, one having had an intracranial haemorrhage. These five patients seem more likely to belong to the 'acute' than to the chronic group, and are referred to as 'probably acute' cases. The other two indeterminate cases could not be allotted to either group.

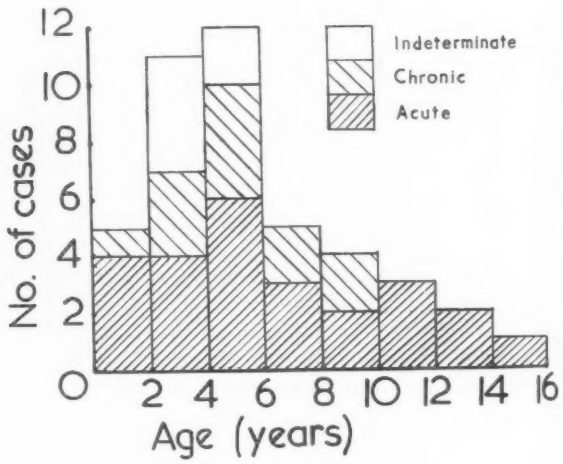

FIG. 1.

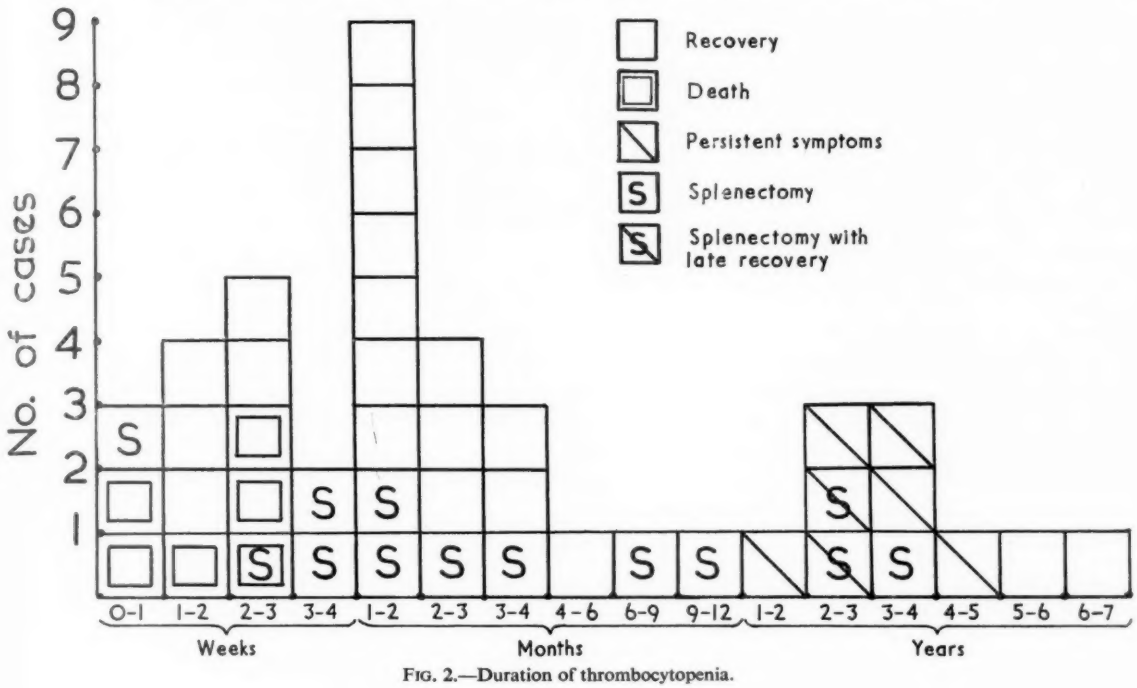

FIG. 2.—Duration of thrombocytopenia.

Acute Cases

Of these 24 children, 12 had mild and 12 severe symptoms, i.e. extensive ecchymoses, severe epistaxis, or spontaneous bleeding of varying severity from other sites. Six of the severe cases died.

All the remaining 18 children made a complete and spontaneous recovery, 11 within six weeks and all but one within three months of the onset of symptoms. In this latter case mild symptoms lasted for six months, after which there was a clinical and haematological remission which has lasted five years.

All cases were followed for over 12 months from the time of remission, 13 for periods of two to five years. There were no relapses once the platelet count had risen above 200,000 per c.mm. except in one case. This boy had apparently recovered completely from acute idiopathic thrombocytopenic purpura within three months; five months later, when his platelet count was 300,000, some spontaneous bruising appeared over a period of three weeks. He quickly recovered, however, and nine months later remains symptom-free.

Symptoms appeared quite suddenly, and all cases but two were seen within two weeks of their first symptoms. In several cases all clinical manifestations cleared after a few days, and in no case was the severity of the disease in the first month exceeded later.

Six patients in this group did not recover; three died from uncontrollable haemorrhage, and three from intracranial bleeding. One boy had a splenectomy the day before he died; he had had an intracranial haemorrhage shortly before admission in the third week of illness. We may conveniently mention here the only other child in the whole series who had any serious complication, a boy in the 'probably acute' group who had an intracranial haemorrhage in the third week of his illness. Splenectomy later cured the idiopathic thrombocytopenic purpura but he remains blind and hemiplegic. All these children had severe skin and mucosal bleeding before their major haemorrhages, and all the major haemorrhages occurred within three weeks of the onset of symptoms.

Intracranial bleeding in idiopathic thrombocytopenic purpura is commonly fatal, and hence, although one of these children survived, we shall for convenience refer to this group of seven patients as 'fatal cases'.

The platelet count in five of the 17 patients who recovered remained quite low for periods of three to five weeks after symptoms had ceased, but in the other 12 the symptoms continued until the platelet count neared 200,000. In general there was no correlation between the platelet level and the severity of symptoms, and in some fulminating cases which died within a few days after the first symptoms the

platelet count did not fall below 90,000. McLean, Kreidel and Caffey (1932) also commented on the high platelet count found in some of their fulminating cases.

Chronic Cases

Of the 12 patients whose symptoms continued for over six months, nine had symptoms for over two years. Of the other three, one still has symptoms after 12 months, while two were cured by splenectomy after six and a half and 12 months respectively.

The onset of symptoms was usually less sudden than in acute cases. This is illustrated by the fact that nine chronic cases had had symptoms for nine months or more before seeking medical advice. In two girls, however, the illness began suddenly and they were seen a few days later; their progress was at first similar to that of an acute case, but the stage of improvement which began after a few weeks was prolonged for over 12 months in one case and for five years in the other.

The severity of symptoms varied greatly. One little boy had very mild bouts of bruising which began at the age of 2 years, and continued for six years; since then he has been symptom-free for two years. The diagnosis was made only when he attended because of an unrelated condition. His platelet counts were in the range of 100 to 120,000 while bruising occurred, but have been over 250,000 since it ceased. Two patients required transfusion because of severe epistaxis, but no child had any graver bleeding.

The six cases besides the little boy just mentioned who did not undergo splenectomy have all tended to improve, some after a few months and others after some years, during which there was little change in the clinical features. Only one, however, appears to have recovered completely so far. This is one of the girls referred to above who had moderately severe symptoms of sudden onset at the age of 5 years, followed by milder recurrent attacks during the next five years. Her symptoms improved, and ceased at the age of 10 years; at the age of 15 years she remains well, and menstruates normally.

In three cases which, on the whole were improving, the platelet counts during bouts of bruising were between 100,000 and 200,000 per c.mm., but during remissions the platelet count rose to over 200,000 per c.mm. The rule observed in acute cases—that relapse rarely follows a platelet count of over 200,000—does not apply to chronic cases.

Five chronic cases underwent splenectomy. Only three had an immediate and permanent cure and were well one to four years later. In the fourth case symptoms and thrombocytopenia ceased about two years after operation, and the child remains well three years later, while the fifth has improved steadily during the 15 months since splenectomy.

Indeterminate Cases

Seven cases underwent splenectomy within four months of the onset of symptoms. All were cured symptomatically and haematologically immediately after operation and are well one to 13 years later, except for the boy who had intracranial bleeding.

Prognosis

Some features which may help the assessment of prognosis are discussed.

Onset of Symptoms. A history of a well-defined onset was obtained in nearly all acute cases, but in only two out of 12 chronic cases. Of 24 cases with a well-defined onset, only two did not recover or die within six months.

Antecedent Infections. An infective illness preceding the appearance of purpura by three weeks or less was noted in 12 out of 22 acute and 'probably acute' cases which recovered, and in four of the seven fatal cases; this history appears to be of little help in determining the possible seriousness of a case. A history of antecedent infection was not obtained in any chronic case; the onset, however, was usually so insidious that it is possible that the relation of a mild infection to the purpura may not have been appreciated by the parents.

As a generalization one can say that if an infection has occurred during the three weeks preceding the appearance of purpura then the disease has been of sudden onset and, therefore, is likely to run a relatively short course.

Clinical Features. Spontaneous bleeding from more than one site (six cases out of seven) and extensive ecchymoses (seven out of seven) occurred before the final haemorrhage in the fatal cases, and these two signs are of considerable prognostic importance.

Splenomegaly was equally uncommon in acute and chronic cases.

Urticaria occurred in seven of 41 children. It was not correlated in any way with the course of the disease.

Eosinophilia. Schwartz and Kaplan (1950) claimed that a bone marrow eosinophilia of over 5% indicated a good prognosis, but others (Newton and Zuelzer, 1951) have denied this, or have thought the correlation only slight (Presley, Best and Limarzi, 1952).

TABLE

Author	No. of Cases Reported	Deaths	Time of Death	Minimum No. of Cases of Duration Over 1 Month	Cases of Duration Over 1 Month with Splenectomy	Cases of Duration Over 1 Month without Splenectomy
McLean *et al.* (1932)	21	4	3 in first mth. 1 at 13 mth.	5	2	3
Clement and Diamond (1953) ..	90	2	1 fulminating 1 at 2½ yr. (nephritis)	55	23	32
Newton and Zuelzer (1951) ..	42	3	3 fulminating	13	6	7
Present	43	6	6 in first mth.	33	9	24
Total	196	15	13 in first mth.	106	40	66
Stroebel *et al.* (1949)	31	0				
Evans and Perry (1943) ..	25	4	All presented with fatal haemorrhages			
Presley *et al.* (1952)	26	0				
Total	278	19				

In the present series the bone marrow was examined in 15 cases, and an eosinophilia was found in nine of them. Rather fewer than 50% of all the cases had an eosinophilia in the peripheral blood. There was no close correlation between blood and marrow eosinophilia, a connexion suggested by Hirsch and Dameshek (1951) but which Schwartz and Kaplan (1950) and Presley *et al.* denied.

Neither blood nor marrow eosinophilia was in any way correlated with the course of the disease or with the response to splenectomy in survivors, except that six of the seven fatal cases had no peripheral eosinophils. The two children with the highest eosinophilia had splenectomies; one was cured at once, but in the second case the symptoms were only slightly improved.

Platelet Levels. Platelet levels in the first three weeks have not had any prognostic significance.

Discussion

We have combined with the figures of the present series those from six of the articles which provide adequate information about the course of the disease in children (McLean *et al.*, 1932; Stroebel, Campbell and Hagedorn, 1949; Clement and Diamond, 1953; Newton and Zuelzer, 1951; Evans and Perry, 1943; Presley *et al.*, 1952). This gives a total of 278 cases of idiopathic thrombocytopenic purpura in children, of whom 19 died (Table). One died after persistent and severe bleeding had continued for 13 months despite splenectomy, another from chronic nephritis; the remaining 17 children all died within one month of the onset of symptoms.

It is not possible to deduce exactly the duration of illness in all these children but, of 196 cases in these series where detailed information is given, at least 106 cases had symptoms for over a month. In the 196 cases there were 15 deaths, 13 in the first month of illness.

Of these 106 cases, 40 underwent splenectomy; 66 cases, therefore, had symptoms which lasted for more than a month (48 of them for over six months) but did not undergo splenectomy. None of them died from idiopathic thrombocytopenic purpura.

The important points are the facts that nearly all the deaths occurred in the first month of the disease, and that no fatal haemorrhages occurred suddenly in patients who had had symptoms for over six months and fall into our chronic group.

We conclude from these observations that in cases seen in the first month of illness the risk of serious complications is appreciable, but that patients who survive this period will, more often than not, undergo complete remission in six months or less, and run much slighter risk of severe complications.

The risk of splenectomy in the acute stages is great (Wintrobe, 1951) and we suggest that all seen in the first month of illness, especially those who have spontaneous haemorrhages, should be given treatment including A.C.T.H. or cortisone in adequate doses (Dameshek, 1952); 50% of cases will undergo remission on such regimes (Limarzi and Best, 1953) and even if remission is incomplete the danger of serious bleeding may be avoided.

In the period one to six months after onset, an expectant policy can be safely adopted, and splenectomy is not indicated, except in the occasional patient whose symptoms are worsening and a

chronic course seems likely. Splenectomy should certainly be avoided if symptoms are clearing even if platelets remain low in number. After six months splenectomy should be considered, and the decision to operate should depend on the degree of disability produced. The operation should not be carried out merely through fear of sudden disastrous haemorrhage, as the risk of such bleeding is remote and probably of the same order as the risk of splenectomy.

Summary

The mortality from acute idiopathic thrombocytopenic purpura is appreciable: in the more severe cases (extensive bruising and bleeding other than mild epistaxis) immediate treatment is indicated. Cases of acute onset which survive the first month nearly all recover spontaneously within six months, the majority within three months.

The mortality from chronic idiopathic thrombocytopenic purpura is very small; in such cases splenectomy should be considered only with regard to the degree of disability produced by the symptoms and not because of a very slight chance of the sudden occurrence of grave haemorrhage.

The best guide to the length of course which a case of idiopathic thrombocytopenic purpura is likely to run is the mode of appearance of symptoms and the presence or absence of a history of antecedent infection.

The haematological findings we have discussed have been of little prognostic value.

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Addendum

Since the above paper was presented for publication we have read an article entitled 'Splenectomy for Idiopathic Thrombocytopenic Purpura'* (Simpkiss and Cathie, 1954), which covers many of the points discussed above and contains several similar conclusions.

* Simpkiss, M. J. and Cathie, I. A. B. (1954). *Gt. Ormond St. J.*, **7**, 9.

CHRONIC GENERALIZED OEDEMA AND HYPOPROTEINAEMIA OF OBSCURE ORIGIN

BY

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Scattered through the literature of the world are a few case reports of chronic generalized oedema with hypoproteinaemia, not associated with defective protein intake, or with an obviously increased loss of protein, such as occurs in albuminuria. Some of these have proved to be associated with changes in the liver, and therefore presumably with protein synthesis. Some of this group, in addition, had steatorrhoea. The causes of hypoproteinaemia were well reviewed by Melnick and Cowgill (1937).

Thompson, McQuarrie and Bell (1936) described a 2-year-old girl with oedema and hypoproteinaemia, which did not respond to a high-protein diet. The total serum proteins were 3·4 g. per 100 ml. (albumin 1·9 g., globulin 1·5 g.). The nitrogen balance was consistently positive. The fact that after transfusion the fall of the serum protein level was very gradual suggested that an abnormal destruction of protein was not the cause of the hypoproteinaemia. At necropsy she had widespread atrophy of hepatic cells, confined chiefly to the intermediate and peripheral areas of the liver lobules, the central zones being spared. They termed the condition 'primary atrophy of the liver of unknown aetiology'. This is apparently the same patient as that described in another paper (Thompson, Ziegler and McQuarrie, 1932).

Warfield (1936) described a 49-year-old woman with generalized oedema, a large liver but normal plasma proteins.

Salvesen and Bøe (1937) described a 31-year-old woman with chronic oedema, ascites, large liver and normal renal function tests. There was achlorhydria. The total serum proteins were normal (6 to 7·5 g. per 100 ml.), but the albumin was reduced (2·8 to 3·3 g. per 100 ml.). The serum globulin was 2·7 to 4·7 per 100 ml. The oedema persisted for the seven months for which she was observed.

Schick and Greenbaum (1945) described a child of 11 years old who had had recurrent oedema from the age of 12 weeks. Her mother had had oedema, possibly of nutritional origin. The girl had hypoproteinaemia (total serum proteins 3·3 g. per 100 ml.; albumin 2·5 g., globulin 0·8 g. per 100 ml.). The urine, blood pressure, and renal function tests were normal. The liver function tests were not quite normal. The serum alkaline phosphatase was 27 King-Armstrong units, the hippuric acid test was borderline, and the glucose tolerance curve was flat. The gamma globulin content of the serum was greatly reduced. A high-protein diet made no difference to the oedema or to the serum protein content.

Jonsson and Lagercrantz (1950) described an 18-month-old boy with oedema, hypoproteinaemia and loose stools, but without steatorrhoea. There was no anaemia. The total serum proteins were 3·1 g. per 100 ml. Electrophoresis showed the albumin to be 30·9%, alpha globulin 12·8%, beta globulin 42·8%, gamma globulin 13·5%, fibrinogen 0·29%. The thymol turbidity, Takata-Ara and alkaline phosphatase tests were normal. The amino-acid absorption curve was normal. At necropsy there was a diffuse fatty degeneration of the liver, with an interstitial fibrosis.

Binger and Keith (1937a, b) described a 62-year-old man with chronic oedema, hypoproteinaemia (total serum proteins 3·6 g. per 100 ml., with an albumin globulin ratio of 1 : 1·6), a low serum calcium and steatorrhoea. At necropsy he had interstitial hepatitis. All sections of the pancreas showed almost complete atrophy of acinous tissue. This corresponded to what Hantelmann (1931) termed 'lipomatous pseudohypertrophy of the pancreas'. Lumb and Beautyman (1952) described a similar condition in a 4-week-old baby, who presented with anaemia, oedema, steatorrhoea, hypoproteinaemia (total serum proteins 5 g. per 100 ml., albumin 2·68 g., globulin 2·32 g. per 100 ml.), and absence of trypsin in the stools and duodenal juice. At necropsy the glandular tissue of the pancreas was almost completely replaced by fat,

with only a small quantity of granular material in the centre. There was a complete absence of acinar elements, which were replaced by normal adult adipose tissue. There was no increase of fibrous tissue, and the islets were normal. They termed the condition 'hypoplasia of the exocrine tissue of the pancreas'.

In the cases described by both Ødegård (1948) and Jones (1949), in addition to cystic fibrosis of the pancreas, there was fatty degeneration of the liver. The former gave very few details about his two cases.

Jungmann (1922) described a man of 28 with chronic oedema and hypoproteinaemia (total serum proteins 3·9-5·0 g. per 100 ml.) with enlarged parotid glands, steatorrhoea and absence of trypsin in the duodenal juice. He rapidly lost oedema when given a sodium-free diet. He had a pituitary tumour, which was presumed to be the cause of the trouble.

Mussio-Fournier, Castiglioni and Anido (1934) described a 38-year-old patient with diarrhoea, oedema and hypoproteinaemia. Johansen (1938) described a 16-year-old girl with oedema, a large abdomen, wasting and infantilism, with hypoproteinaemia (total serum proteins 3·6 g. per 100 ml., albumin 2·1 g., globulin 1·1 g.), hypocalcaemia (serum calcium 7·8 mg. per 100 ml.) and with normal liver and renal function tests. No fat balance tests were carried out on these two cases, but they could well have had chronic steatorrhoea.

Salomonsen (1945) described a 2-year-old girl with persistent oedema, diarrhoea, hypoproteinaemia and normal renal function. No fat balance was performed, though simple analysis did not show excess of fat in the stools.

Story and Sagild (1953) described a fatal case of 'Whipple's disease'—steatorrhoea, arthralgia, elevation of serum glycoproteins, and hypoproteinaemia, with foamy cells in the mesenteric lymph nodes and intestinal mucosa. Their patient had oedema, and the total serum proteins were 3·6 g. per 100 ml. (albumin 2·1 g.).

There remain a variety of case reports of very chronic generalized oedema and hypoproteinaemia of obscure origin. In most of these cases liver function tests were carried out and found to be normal, but in none of them (except in the case of Homburger and Petermann, 1949) were fat balance studies carried out in order to exclude steatorrhoea. Homburger and Petermann described a remarkable family exhibiting what they termed 'familial idiopathic dysproteinaemia'. The syndrome included oedema of the legs, ulcers in the males, functional vascular changes in the females, alterations in the plasma proteins, congenital malformations of the thoracic cage and abnormality of occipital hair distribution, and a high incidence of stillbirths. In one case the plasma proteins were low in spite of a positive nitrogen balance.

Keith (1932) mentioned five cases of unexplained oedema aged 9 to 69 years. Serum protein estimations were carried out in one only, the total being 4·6 g. per 100 ml. No other information was given.

Myers and Taylor (1933) described a man of 51 with generalized oedema of many years' duration, with a history of a six months' episode of oedema at the age of 4 years. The total serum proteins varied between 3·3 and 4·0 g. per 100 ml. A high protein diet was without effect. The laevulose tolerance was slightly reduced, but other liver function tests were normal. The serum calcium was 7·9 mg. per 100 ml. The serum amino-acid content was above normal, namely, 6·51 to 8·41 mg. per 100 ml. He had achlorhydria, a positive nitrogen balance and no excess of nitrogen in the stools. The hypoproteinaemia was ascribed to defective synthesis of plasma proteins.

Grabfield, Driscoll and Gray (1934) described a 32-year-old woman with chronic oedema, with a high total serum protein (8·3 g. per 100 ml.) but with low serum albumin (1·7 g. to 3·7 g.). The nitrogen balance was positive. There was a pelvic mass which was thought to be irrelevant.

Cope and Goadby (1935) described a 20-year-old man with normal blood pressure, normal haemoglobin and renal function tests, but with total serum proteins of 4·6 g. per 100 ml. (albumin 3·1 g., globulin 1·5 per 100 ml.). The nitrogen balance was positive, and a high-protein diet had no effect. Oedema was still present a year after the onset.

Binger and Keith (1937a, b) described a 35-year-old woman with chronic oedema and hypoproteinaemia and reduction of serum albumin. The total serum proteins were 2·7 g. per 100 ml. No fat balance studies were made.

Rytand (1942) described a 24-year-old woman with chronic hypoproteinaemia and oedema. The total serum proteins varied between 3·0 and 4·7 g. per 100 ml., the albumin being 2·7 to 2·9 g. per 100 ml. The oedema lasted for more than eight years. The nitrogen balance was positive. The liver function tests were normal. There was some eosinophilia and reticulocytosis. A high-protein diet and amino-acids by mouth had no effect.

Albright, Bartter and Forbes (1949) studied a 19-year-old man with generalized oedema of two years' duration. His total serum proteins were 4·0 g. per 100 ml. (albumin 2·6 g.), and renal and liver function tests were normal. A liver biopsy

showed no abnormality. He was not anaemic. His serum calcium was 7·0 mg. per 100 ml., and the phosphorus 3·5 mg. A careful study of the fate of albumin when injected intravenously showed that the defect lay in an increased rate of destruction rather than in a decreased rate of synthesis. None of the injected albumin was lost in the urine.

Bound and Hackett (1953) described an infant, aged 1 month, with hypoproteinaemia from birth, with a virtual absence of gamma globulin. There was intermittent amino-aciduria. His haemoglobin was 13 g. per 100 ml.: serum proteins 4·0 g. per 100 ml. (albumin 2·5 g.): the serum bilirubin, alkaline phosphatase, thymol turbidity and cholesterol were normal. An amino-acid chromatogram showed excess of glycine and alanine, threonine and a trace of cystine. The serum amino-acid nitrogen was 8·6 mg. per 100 ml. He suffered from recurrent staphylococcal infections. It was thought that the reduction of gamma globulin was against the possibility of liver disease. There was a similar history in a sibling, whose total serum proteins were 3·0 g. per 100 ml., and whose liver at necropsy showed extensive fatty degeneration with a portal cellular reaction.

Below are case histories of two children who were under our care in the Children's Hospital, Sheffield.

FIG. 1.—Photograph of Case 1 showing loss of hair, and signs of ariboflavinosis.

Case Reports

Case 1, R.P. This boy was admitted at the age of 5 years and 11 months with a history of oedema and listlessness of one week's duration. He had attended school for the last 12 months without missing a single day. He had had a good mixed diet, and no previous illness of note. There was no relevant family history.

He was a pale boy with ascites and generalized oedema, including oedema of the face, sacrum, genitals and lower limbs. There were a few petechiae on the abdomen, arms and legs—for which no explanation was found. Stools were normal on admission, but as a result of deliberately looking for it, steatorrhoea was found. Subsequently, three months after admission, the stools became loose and offensive. He became anaemic and was transfused several times with whole blood and plasma. In each case a good diuresis resulted, but fluid rapidly reaccumulated.

The urine was consistently normal chemically and microscopically. The serum proteins were reduced: the average of 22 serum protein estimations was 4·5 g. per 100 ml.: the average of five serum albumin and globulin estimations was 2·6 g. and 1·4 g. per 100 ml. respectively. A nitrogen balance test was positive, but there was a high faecal nitrogen loss (at a time when he had diarrhoea). The erythrocyte sedimentation rate and the kidney and liver function tests were normal. There was no trypsin in a sample of duodenal juice, but the radiographs of the chest revealed no abnormality. A high-protein diet had no effect, oedema persisted, and he was discharged in spite of it.

He was re-admitted four months later with gross oedema, an almost complete loss of hair, and severe ariboflavinosis, with redness and soreness at the inner and outer canthus of the eyes, around the nostrils, ears, angle of the mouth and the scrotum (Fig. 1). This responded rapidly to treatment with riboflavin, but subsequently relapsed. A month after admission he became jaundiced, and a diagnosis of serum hepatitis was made. The jaundice lasted for four months.

He was discharged with persistent oedema, but was re-admitted acutely ill at the age of 6 years and 11 months and died two weeks later.

At necropsy it was found that he had terminal bronchopneumonia, but no changes suggestive of cystic fibrosis of the pancreas. There was no abnormality of the salivary glands or of the mucous membrane of the respiratory tract. The pancreas appeared to be infiltrated with fat, and the lobules were widely spread, with fat globules scattered through the gland. The acini appeared to be collapsed and atrophic. The surface of the liver was slightly irregular and it was firm on section. It showed intense fatty change and swelling of the parenchymal cells. The wall of the stomach and jejunum was thickened. In the intestinal tract there was an increased cellularity beneath the surface epithelium and in the villi. The proximal tubular cells of the kidney and the tissue of the loops was swollen and vacuolated.

There was an abnormal number of large fat globules in the tubular cells.

BIOCHEMICAL INVESTIGATIONS. The urine was consistently normal on repeated examinations, except for the presence of bilirubin and urobilinogen during the attack of jaundice.

An Addis count gave 500,000 red blood cells per 24 hours and 180,000 white blood cells per 24 hours.

The blood urea level was 15-30 mg. per 100 ml. (repeated estimations). The urea clearance test, hippuric acid test, and galactose tolerance test were all normal. A thymol turbidity test before jaundice gave a result of 1 unit. The Takata-Ara test was negative. The serum alkaline phosphatase level before jaundice was 5-11 King-Armstrong units.

The bilirubin level during jaundice was 2·7-4·3 mg. per 100 ml., chlorides (as NaCl) 635 mg. per 100 ml., cholesterol 120 mg. per 100 ml., proteins (total) 3·3-4·2 g. per 100 ml. (albumin 1·8-3·5 g. per 100 ml., globulin 0·6-2·1 g. per 100 ml.).

Fractionation and electrophoresis (Professor Nicholas Martin), when the total serum proteins were 4·2 g. per 100 ml., showed a moderate increase of beta globulin and a slight increase of gamma globulin.

	Electrophoresis	Fractionation
Albumin	43·5%	36%
Alpha globulin	15·5%	23%
Beta and gamma globulins	38·5%	40%
T. globulin	2·0%	

A nitrogen balance was positive.

Total intake (6 days)	45·7 g. nitrogen.
Output in urine	5·3 g.
Output in stools	22·0 g.
Retention	18·4 g.

No trypsin was found in the duodenal juice. An amylase estimation showed that 6·5 g. dextrose was liberated per 100 ml. (upper limit of normal).

The erythrocyte sedimentation rate on admission was 6 mm. per hour.

The haemoglobin on admission was 8·9 g. per 100 ml., red blood cells 3,000,000 per ml. P.C.V. 37 ml., M.C.V. 116, halometer reading 6, M.C.H. 27·5, and M.C.H.C. 23·8. Prothrombin time was normal. The capillary fragility test (Wintrobe) was normal.

The Wassermann reaction was negative.

Tuberculin tests were negative.

Blood pyruvic acid was 0·95 mg. per 100 ml.

An E.C.G. was normal, as also was a radiograph of the chest.

The stools two months after admission were semi-solid, greasy, and contained 50 fat droplets per high power field, fairly large numbers of fatty acid crystals, a few extracellular starch granules and many fragments of undigested vegetable matter. The stools continued to show excess of fat, but no fat balance was performed.

The oedema fluid (peritoneal) was analysed as follows:

Protein	1·3 g. per 100 ml.
Sodium	310 mg. per 100 ml.
Chloride (as NaCl)	690 mg. per 100 ml.
Potassium	18 mg. per 100 ml.
Urea	20 mg. per 100 ml.
Cholesterol	50 mg. per 100 ml.

Case 2, D.C. This boy was admitted to a surgical ward at the age of 2 years on account of oedema of the legs for two weeks without any other symptoms. Till then he had been perfectly well, and had had no previous illnesses of note. There was no relevant family history. The boy had had a good mixed diet and weighed 27 lb.

He had pitting oedema of the lower limbs, genitals and sacrum. The oedema was more marked in the right leg than in the left. The abdomen was slightly protuberant, but there was no sign of free fluid. The blood pressure was normal (80/45 mm. Hg), and there were no other abnormal physical signs.

Laboratory investigations showed that the urine was consistently normal. He had hypoproteinaemia, the average of 27 readings for the total serum proteins being 3·6 g. per 100 ml. The average figures for the serum albumin and serum globulin were 2·0 g. and 1·5 g. per 100 ml. respectively. The erythrocyte sedimentation rate was normal, there was no anaemia, and the kidney and liver function tests were normal. The nitrogen balance was positive. Stools were repeatedly examined by the naked eye, and microscopic examination for excess of fat showed no excess of fat globules, but unfortunately as a result of undue reliance on these findings for excluding steatorrhoea, no fat balance was performed at this time.

The oedema persisted, and he was discharged on a high-protein diet with a diagnosis of hypoproteinaemia of unknown cause. The high-protein diet made no apparent difference, the oedema being unchanged. He was re-admitted at the age of 3 years 2 months, 3 years 10 months and 4½ years for cellulitis of a lower limb, which in each case responded promptly to antibiotic treatment. In the last of these spells in hospital (at the age of 4½ years), a fat balance test was performed in order to exclude steatorrhoea, though the stools had remained normal macroscopically and microscopically. Definite steatorrhoea was demonstrated, and subsequently some stools were found to be pale and bulky, but no diarrhoea or looseness occurred. A gluten-free diet was given for four months, without any effect on the oedema or serum proteins, and it was discontinued.

Bile salt ('bilron') in a dose of 0·6 g. three times a day before food had no effect on the serum proteins. He was then given five plasma transfusions, totalling 2,000 ml., and the serum proteins were thereby restored to normal and the oedema dispersed, but in a few days the serum protein had returned to the previous figure, the oedema recurring.

The child has now attended school regularly for nine months (present age 5 years 9 months), though slight oedema has persisted. His weight is 54 lb.

BIOCHEMICAL INVESTIGATIONS. At the age of 2 the urine specific gravity was up to 1,029: the urine was consistently normal chemically and microscopically. The urea (single estimation) concentration was 1·05 g. %, amino-acid nitrogen 90 mg. %. An amino-acid chromatogram was normal, as also was a concentration test.

The stools were normal macroscopically, and microscopically showed less than 1 fat globule per high power

field. Tryptic activity was seen up to a dilution of 1 in 640.

Serum protein (total)	3·3 g.-4·1 g. per 100 ml. (7 estimations)
Albumin	1·4 g.-1·8 g. „ „ „ „ „
Globulin	1·2 g.-1·5 g. „ „ „ „ „
Fibrinogen	0·45 g. „ „ „ „ „
Cholesterol	195-298 mg. „ „ „ (3 estimations)
Inorganic phosphorus	4·4-6·1 mg. „ „ „
Calcium	9·3 mg. per 100 ml.
Alkaline phosphatase	4-13·8 units (Jenner and Kay)
Sodium	320-348 mg. per 100 ml.
Chlorides	597-648 mg. „ „ „
Potassium	16·9 mg. „ „ „
Amino-acid nitrogen	7·0 mg. „ „ „

The blood urea level was 20-28 mg. per 100 ml. (three estimations). Thymol turbidity was less than 1 unit. The erythrocyte sedimentation rate was 3-11 mm. per hour (micro.), the haemoglobin 15·1 g. per 100 ml., the M.C.H.C. 33·5, and R.B.C. 4,000,000 per c.mm.

A nitrogen balance was positive.

Total intake in 3 days	22·5 g.
Urinary output	15·5 g.
Output in faeces	3·0 g.
Retention	4·0 g.

Between the ages of 4½ and 5½ years fat balances gave the following results: (i) 74% retention of total intake of 195 g. (3 days), (ii) 85% retention, (iii) 86% retention.

Nitrogen balances were positive as follows:

Total intake in 3 days	27·4 g.
(i) Urinary output	19·75 g.
Output in faeces	4·13 g.
Retention	3·5 g.
(ii) Total intake	18·4 g.
Total output	12·6 g.
Retention	5·8 g.

An amino-acid nitrogen curve after taking 5 g. gelatin, 27 g. 'casilan', juice of one orange and sugar gave:

Fasting level	4·5 mg./100 ml.
½ hour	5·3 „ „ „
1¼ „	6 „ „ „
2¾ „	5·6 „ „ „
5 „	5·6 „ „ „

Amino-acid chromatograms (Dr. Bickel) showed (i) faint traces of glycine, alanine, glutamine and cystine; (ii) only traces of cystine; (iii) normal excretion of glycine, alanine, glutamine, histidine; (iv) excretion of cystine marked, but within normal limits, and excretion of glycine, serine, alanine, glutamine and glutamic acid normal or perhaps a little low.

Electrophoresis (Professor Nicholas Martin) showed a negligible amount of gamma globulin.

Bromsulphthalein excretion was normal: at 5 minutes 39% dye was excreted and at 30 minutes nil.

A glucose tolerance curve was normal.

Serum proteins (g. per 100 ml.) were analysed as follows:

	Total Protein	Albumin	Globulin
Before plasma transfusion	3·0–4·6	1·2–3·0	1·0–2·2
2 days after „	7·6	3·7	3·9
4 „ „ „	6·5	3·5	3·0
8 „ „ „	4·5	2·9	1·6
19 „ „ „	4·4	2·2	2·2

Serum amino-acids (mg.) were estimated by Dr. Bickel as follows:

Amino-acid	Patient's Level	Normal Level (Krebs, 1950)	S.D.
Phenylalanine	1·15	1·38	0·32
Tyrosine	0·7	1·48	0·37
Valine	2·6	2·83	0·34
Arginine	2·4	2·34	0·70

Estimation of the total serum lipoids gave 555 mg. per 100 ml.

Serum sodium	352 mg. per 100 ml.
Chlorides	660 „ „ „ „
Potassium	17·8 „ „ „ „
Cholesterol	219 „ „ „ „
Alkaline phosphatase	10·0-14·0 units
Phosphorus	4·7 mg. per 100 ml.
Calcium	10·0 „ „ „ „

Thymol turbidity was less than 1.

The blood urea level was 15 mg. per 100 ml.

The erythrocyte sedimentation rate was 3 mm.

Haemoglobin was 14·5-14·8 g. per 100 ml., P.C.V. 45%, M.C.H.C. 33·5%.

The stools were microscopically normal and showed tryptic activity to a dilution of 1 in 320.

Duodenal juice showed tryptic activity to a dilution of 1 in 320, and amylase to 1 in 80.

A radiograph of a wrist was normal, and a flocculating radiograph for intestinal pattern was also normal.

Discussion

A review of the literature gives a clear indication that at least some cases of chronic obscure oedema are associated with disease of the liver or pancreas, and with a defect of protein metabolism. It was certainly true that in all the cases in which nitrogen balances were performed the balance was positive, and in all the cases in which a high-protein diet was given it was of no avail.

We assumed that in both the children we have described the oedema was due to hypoproteinaemia, and particularly to the reduction of serum albumin, but the cause of the hypoproteinaemia was not clear. The protein intake in both appeared to have been normal before symptoms developed, and a high-protein diet in hospital did not appear to benefit them. In neither case had there been any history of diarrhoea, and naked-eye and microscopic examination of the stools was in both cases normal on admission. Steatorrhoea was found only as a result of specific investigation by means of fat balance tests, and we feel as a result of this experience that no investigation of obscure oedema is complete unless fat balance tests are performed. Diarrhoea did develop in one case (R.P.) after admission and later ariboflavinosis developed as a result, but at least in the early part of his illness it seemed unlikely, in

the absence of diarrhoea, that the hypoproteinaemia was merely due to defective absorption of protein.

The level of certain amino-acids in the serum was low in one case, but electrophoretic analysis threw little light on the problem, except that the virtual absence of gamma globulin in one case (D.C.) helped to explain the recurrent attacks of cellulitis. We concluded that we did not know the cause of the hypoproteinaemia in these children.

The common cause of steatorrhoea in children is either coeliac disease or cystic fibrosis of the pancreas, but we felt in both cases that the cause of the steatorrhoea lay in some other condition. The necropsy findings in one case (R.P.) corresponded with those described by Lumb and Beautyman (1952) under the term 'hypoplasia of the exocrine tissue of the pancreas'. The second case (D.C.) differed from coeliac disease in the history and clinical findings, the lack of response to a gluten-free diet, and the absence of the characteristic radiological picture. Cystic fibrosis of the pancreas was virtually excluded by the finding of a normal quantity of trypsin in the duodenal juice, and the absence of lung complications. The cause of the steatorrhoea was therefore unknown.

The development of acute ariboflavinosis in R.P. was of particular interest.

Summary

After a review of the literature, two cases of obscure generalized oedema with hypoproteinaemia and steatorrhoea are described. One child died, and was found to have fatty infiltration of the pancreas and atrophic acini, without cystic fibrosis. The other child does not appear to have either cystic fibrosis of the pancreas or coeliac disease. The cause of the hypoproteinaemia was not determined.

We wish to thank Professor H. A. Krebs, F.R.S., for his helpful advice in the study of these cases and for reading through this paper. We also wish to thank Dr. H. Bickel for the amino-acid chromatograms, and Professor Nicholas Martin for the electrophoretic analyses. We are indebted to Dr. J. L. Emery for the post-mortem findings in one case.

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TEMPORARY GENERALIZED OEDEMA OF OBSCURE ORIGIN

BY

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Very few papers have been written about temporary generalized oedema of unknown origin. When one has excluded such obvious causes of temporary oedema as starvation, nephritis, hepatitis, diarrhoea, heart failure, burns, chronic suppuration, excessive hydration, sodium retention due to drugs, or even drug allergy, there remains a group of cases in which oedema develops without apparent cause and disappears with equally little apparent reason.

Some writers have suggested that acute nephritis may occur without albuminuria. Keefer (1939) described a 16-year-old girl who presented with impetigo and generalized oedema with pleural effusions of five days' duration. The blood pressure was raised (150/105 mm. Hg), but the serum proteins were not reduced (total 5·94 g. per 100 ml., albumin 3·2 g.). The renal function tests were normal. All oedema disappeared in 14 days. Keefer ascribed the oedema to increased capillary permeability or pressure. Brod (1949) described a 28-year-old man who developed hypertension and oedema without albuminuria. The serum proteins were not estimated. The patient made a complete recovery. Crofton and Truelove (1948) described a girl of 16 who developed oedema and hypertension without albuminuria but with normal plasma proteins. They reviewed the literature, giving several references to similar cases. Other references to this condition were given by Keefer (1939) and by Salvesen and Bøe (1937).

One of the cases of obscure oedema described by Binger and Keith (1937) may have fallen into this category, for her blood pressure was 140/90 mm. Hg on admission, but it is not clear whether it remained at this figure. The patient was a 49-year-old woman who had oedema for just over three months. The only abnormality noted was hypoproteinaemia (total serum proteins 3·6–4·5 g. per 100 ml., albumin 2·4–2·6 g.). She was discharged free from oedema, but there is no note of whether she was followed up.

Meyer-Bisch (1925) described four adults with generalized oedema who were said to lose their oedema promptly when rested in bed. Three of the four had lowered serum proteins. One had steatorrhoea. All had achlorhydria.

Heimann and Gross (1933) described a nine-week episode of oedema in a 49-year-old man, with normal urine and blood pressure. Serum proteins were not estimated and no further data were available.

Messinger (1946) described an episode of generalized oedema, lasting eight months, in a 27-year-old woman with a previous history of thyrotoxicosis. At the onset of the oedema she gained 20 lb. in a month. The blood pressure, urine and erythrocyte sedimentation rate were normal. The serum proteins were reduced (total 4·7 g. per 100 ml., albumin 2·9 g.). No nitrogen balance was performed. The glucose tolerance curve was slightly flat during the phase of oedema, returning to normal when the oedema disappeared. There was some eosinophilia (19% of 11,600 leucocytes). A high-protein diet was without effect. The oedema disappeared a month after pregnancy began. Messinger suggested that the hypoproteinaemia might have been due to a disturbance of the anterior pituitary, but the evidence for this was very slender.

Hertzog and Faust (1950) described an episode of oedema in a baby, lasting from the age of 2 weeks to 20 weeks. The urine was normal. The total serum proteins were 1·92 g. per 100 ml. (albumin 1·45 g., globulin 0·47 g.). The serum calcium level varied between 6·2 and 7·8 mg. per 100 ml., with a serum phosphorus level of 3·8 to 4·8 mg. per 100 ml. Liver function tests were normal. The protein content of the oedema fluid was 306 mg. per 100 ml., and 75 g. of concentrated sodium-free human albumin raised the total serum proteins by only 0·9 g. per 100 ml. A spontaneous diuresis occurred, the oedema disappeared and the serum proteins returned to normal (6·5 g. per 100 ml.).

The writers suggested that the hypoproteinaemia was due to a temporary abnormality in protein synthesis and catabolism.

Wyngaarden, Crawford, Chamberlin and Lever (1952) described a 10-week episode of generalized oedema in a 3½-year-old boy, developing two weeks after tonsillitis. The case was well investigated. The total serum proteins were 3·14 g. per 100 ml. (albumin 2·37 g., globulin 0·77 g. per 100 ml.). Electrophoretic analysis showed that there was a considerable decrease in gamma globulin, with a slight elevation of the alpha globulins. The erythrocyte sedimentation rate, urea clearance and bromsulphthalein excretion tests were normal. Recovery was uneventful, the total and fractional serum protein values returning to normal.

Below are case histories of two children who were under our care in the Children's Hospital, Sheffield.

Case Reports

Case 1. R.M., a boy, was admitted at the age of 7½ months with a history of oliguria of two weeks' duration, puffiness of the eyes for 19 days, and distension of the abdomen for seven days. There was no previous illness of note.

On examination there was marked generalized oedema with ascites (Fig. 1). The circumference of the abdomen

FIG. 1.—R.M., showing oedema, distension of abdomen, and everted umbilicus.

was 22 in. The heart and blood pressure were normal.

Three weeks after admission he had a spontaneous diuresis and the oedema disappeared, with a loss of 4 lb. in weight, the plasma proteins returning to normal. On follow-up for a period of almost five years there was no recurrence. The total duration of the oedema was therefore approximately five weeks.

INVESTIGATIONS. The methods used are the same as those described in the previous paper on page 507.

The urine was normal chemically and microscopically, with chlorides 260 mg. per 100 ml.

Haemoglobin was 13·3 g. per 100 ml., red blood cells 5,100,000 per c.mm.

The stools on repeated examination were normal macroscopically and microscopically.

Serum protein levels were as follows:

	Total	Albumin	Globulin
	(g. per 100 ml.)		
2 days after admission	4·7	2·8	1·9
6 days after admission	3·8	1·8	2·0
21 days after admission and 2 days after diuresis	5·4	4·1	1·3

Serum cholesterol level 260 mg. per 100 ml., serum alkaline phosphatase 9·7 King-Armstrong units, serum bilirubin 1·3 mg. per 100 ml., serum sodium 335 mg. per 100 ml. Blood urea was 35 mg. per 100 ml. A fat balance (10–day specimen) gave 88·3% fat absorbed.

A nitrogen balance gave a total intake of 47·7 g. nitrogen of which 15·5 g. was excreted in the urine and 4·3 g. in the stools, and 27·9 g. was retained.

The Wassermann reaction was negative, as was the tuberculin reaction.

Case 2. M.H., a boy, was admitted to another hospital at the age of 3 years with a history of generalized oedema of insidious onset of one month's duration, following a cold and sore throat associated with vomiting. On examination at that hospital there was marked generalized oedema including the face, sacrum and lower limbs. The blood pressure was normal (100/70 mm. Hg): the urine was normal and the erythrocyte sedimentation rate was 4 mm. in an hour. The urea clearance test was normal. The oedema persisted, and he was discharged home. He was first seen at this hospital six months after the onset. He had not been free from oedema during this period.

At this time he had slight generalized oedema, including the sacrum and lower limbs, and the eyes were puffy. The blood pressure was normal (110/70 mm. Hg). The urine was normal chemically and microscopically, and the Addis count was normal. The erythrocyte sedimentation rate, blood urea and urea clearance tests were normal. The serum proteins were very low (3·4 g. per 100 ml.). He was discharged after a week with slight residual oedema, a diagnosis of idiopathic hypoproteinaemia being made. He was followed up as an out-patient, and mild oedema persisted.

He was re-admitted at the age of 4 years 1 month for further investigation. He weighed 40 lb., and had slight generalized oedema. Laboratory investigation showed hypoproteinaemia as before, with a positive nitrogen balance and a normal fat balance. Liver function tests were normal. The plasma showed decreased levels of tyrosine, tryptophane, arginine and valine. (It is interesting to note that the plasma of a similar patient, shown to the writers by Drs. Allibone and Prosser, showed the same decreased plasma amino-acid content, with, in addition, a decreased lysine content.)

A spontaneous diuresis occurred two weeks after admission, with loss of the oedema and a return of the serum protein to normal. He lost 3 lb. in weight. The total duration of oedema was approximately 14 months.

He has been followed up continually since his discharge, and there has been no recurrence. When last

seen (aged 5½) he was well and free from oedema, and attending school regularly.

INVESTIGATIONS. At 3½ years of age the urine was normal chemically and microscopically with a specific gravity of 1,029 on repeated specimens. An Addis count gave: red cells 452,400 per 24 hours, white cells 638,400 per 24 hours, protein 26·6 mg. per 24 hours. Urea clearance were (1) 109% normal and (2) 121% normal.

Total serum proteins were 3·4 g. and 4·3 g. per 100 ml. (albumin 2·1 g., 3·0 g., globulin 1·3 g., 1·3 g.).

Blood urea was 23–24 mg. per 100 ml. The erythrocyte sedimentation rate was 7 mm. per hour (micro.).

Three amino-acid chromatograms were taken by Dr. Bickel, the first at 3 years 7 months. It showed slightly increased excretion of cystine, alanine and glutamine, normal excretion of glycine, glutamic acid and histidine, traces of tyrosine, the leucines and valine. The total ninhydrin colour was 110 taurine units (normal up to 85). The pattern was not that of Lignac-Fanconi disease but resembled the pattern of renal amino-aciduria as in Wilson's disease. The second chromatogram at the age of 3 years and 8 months showed normal excretion of glycine, alanine, glutamine, and histidine, with traces of tyrosine, and a normal pattern. At 4 years 1 month the urine was normal, and an amino-acid chromatogram (Dr. Bickel) showed a normal pattern.

Wassermann and tuberculin reactions were negative.

Haemoglobin was 12·6 g. per 100 ml. and red cells were 4,400,000 per c.mm. The erythrocyte sedimentation rate was 13 mm. per hour (micro.), and the blood urea 21 mg. per 100 ml.

Total serum proteins were 3·0 g. per 100 ml. (albumin 2·2 g., globulin 0·8 g.). Serum lipoids were 340 mg., serum cholesterol 94 mg., serum sodium 350 mg. and serum potassium 13 mg. per 100 ml. Thymol turbidity was 2·8 units.

On discharge two months later the serum proteins (total) were 5·2 g. per 100 ml. (albumin 3·3 g., globulin 1·9 g.). A nitrogen balance was positive, showing total intake of nitrogen 18·5 g., output in urine 8·5 g., output in stools 2·7 g., total 11·2 g., and retention 7·3 g. A fat balance gave 93·5% retention of intake (three days). The total fat in faeces was 27·6% of dried faeces.

Plasma amino-acids (mg. per 100 ml.) were determined by Dr. Bickel as follows:

Amino-acid	Patients	Controls	
	M.H.	A	B
Phenylalanine	0·66	0·82	0·70
Valine	2·41	2·62	3·18
Tyrosine	0·79	1·35	1·48
Tryptophane	0·51	1·18	1·02
Lysine	—	2·60	2·98
Arginine	1·40	2·14	2·08

There were decreased levels of tyrosine, tryptophane, arginine and valine.

At 4 years 5 months the total serum proteins were 5·9 g. per 100 ml. (albumin 3·8 g., globulin 2·1 g.), and at 5½ years total serum proteins 5·4 g. per 100 ml. (albumin 3·5 g., globulin 1·9 g.) An amino-acid chromatogram was still normal.

Discussion

The two children described presented a temporary oedema with hypoproteinaemia without any apparent reason. They did not fall into the group of cases described by Keefer (1939), Crofton and Truelove (1948), Brod (1949) and others as nephritis without albuminuria, for the blood pressure in our cases was normal and the serum proteins were reduced. We have only been able to find six references to cases which appeared to be similar (Meyer-Bisch, 1925; Heimann and Gross, 1933; Binger and Keith, 1937; Messinger, 1946; Hertzog and Faust, 1950; Wyngaarden, *et al.*, 1952). Only the last two of these papers refer to children.

In both our cases the only significant finding was hypoproteinaemia with a particularly low serum albumin level. The nitrogen balance was positive in both. In one of the children there was a reduction of certain amino-acids in the serum; they were not estimated in the other child. There was no diarrhoea at any stage in either child, and no suggestion of a reduced protein intake or increased protein loss. The nature of the pathological process remains a matter of speculation. The observations are in accordance with the view that the primary disorder concerns the metabolism of the plasma proteins, in particular the albumin and globulin fractions. The fault may be either a reduced rate of production, or a failure of the mechanism controlling the concentration of the proteins in the plasma. It may be that the condition is essentially a mild and reversible form of the chronic oedema and hypoproteinaemia described in the previous paper.

Summary

Two cases of oedema with hypoproteinaemia are described, one lasting for five weeks and the other for 14 months. Recovery in both cases was spontaneous and complete.

It is suggested that the cause in both cases lay in a temporary disturbance of protein metabolism of unknown origin.

We wish to thank Professor H. A. Krebs, F.R.S., for his guidance in the study of these children and for his criticism of this paper. We also wish to thank Dr. H. Bickel for the amino-acid chromatograms.

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COLLODION SKIN OF THE NEWBORN

BY

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Although some superficial desquamation, especially about the flexural creases, is common in the neonatal period, a collodion-like covering of the skin is rare. On this account two cases of collodion skin of the newborn, each of which illustrates a different aetiology, are reported.

Case Reports

Case 1.—Patrick G. was born on December 27, 1952, as a breech delivery and weighed 7 lb. It was the fourth pregnancy, the other children being alive and well except for the elder twin of the second pregnancy who died at 3 weeks of age from congenital hypertrophic stenosis of the pylorus. There was no history of ichthyosis in the family.

At birth the infant cried readily but had a varnished appearance due to an almost complete covering of parchment-like skin. This was thickest over the anterior surface of the thorax and abdomen, less on the posterior surface, and absent over the head where covered with hair. The face was affected, causing a characteristic, unpleasant, immobile expression. The eyelids were sealed together and although the mouth and nostrils were patent they had a wrinkled and fissured appearance. The limbs were similarly affected and movements were restricted; the hair was normal as were the nails beneath their covering. Although the infant appeared immobile in his stiff casing, he had a vigorous cry and sucked well. Warm, sterile olive oil was applied daily to the surface of the body. Within two days the eyelids had partially separated giving a slit-eyed appearance; the eyes were normal. As the collodion-like coating hardened it began to crack, especially about the joints as the infant became more active (Fig. 1A). Likewise longitudinal cracks developed over the trunk, revealing a 'beefy', red appearance beneath. During the next two weeks the false skin peeled off leaving intact and normal skin underneath.

Unfortunately, on the ninth day the left breast became flushed and a suppurative mastitis developed. This infection, caused by *Staphylococcus aureus*, responded to surgical drainage and streptomycin therapy. During the next few weeks three or four fine layers of papery scales desquamated readily from the head and axillae and slightly from the trunk. The infant thrived satisfactorily and at 14 months of age the skin appeared to be perfectly normal. The Wassermann reactions of the mother and child were negative.

Histological examination of the membrane showed it to be composed of condensed layers of keratin. A biopsy of the skin was performed and Dr. J. E. Morison reported that the section showed no significant abnormality. The skin appendages were normally developed except perhaps for a slight dilatation of the orifices of the hair follicles and some slight retention of hyperkeratotic squamous debris.

Case 2. Valerie McC. was born on May 13, 1944, at full term, weighing 6 lb. 1 oz. and the delivery was normal. It was the third pregnancy and the mother's Wassermann reaction was negative. The first infant died after an operation for reduction of congenital dislocation of the hips, and the second died at the seventh day of life with spina bifida. There was no family history of ichthyosis. At birth the patient cried immediately but was noticed to be tightly encased in a yellowish membrane, resembling oiled silk, over the head, body and limbs. Cracks rapidly appeared about the flexures and the covering began to flake off revealing the skin beneath of an angry red colour with a tendency to bleed along the creases of the neck and groins. The hands and feet were slightly oedematous but the nails beneath the covering layer seemed normal (Fig. 1B). The eyelids were sealed together and puckered at the corners but the next day they could be partially separated giving a slit-eyed appearance; the eyes were normal. Warm, sterile olive oil was applied locally and thyroid extract, gr. $\frac{1}{2}$ twice a day, was given for the next two weeks. During the following few days the membranous layer was gradually shed; over the head, although some of the hair came away with the covering substance, normal scalp and hair were left beneath. Likewise the nails remained intact and normal.

The infant fed and thrived well, but on discharge at 3 weeks of age the skin of the abdomen was becoming dry and papery.

At 9 months of age the infant was normal except for the persistence of dry and flaky skin of the groins and abdomen. At 8 years and 9 months of age the child presented typical mild ichthyosis. The skin of the abdomen (Figs. 2*a* and 2*b*) was chiefly affected; the condition was worse in the winter and improved in the summer months.

FIG. 1A.—Case 1, aged 4 days.

FIG. 1B.—Case 2, aged 4 days.

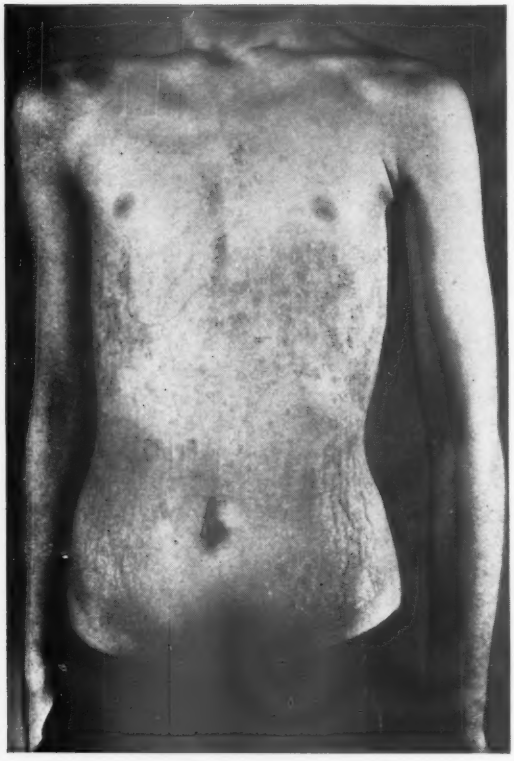
Discussion

Collodion skin of the newborn presents a characteristic picture which was originally described by Perez in 1880. From the character of the membranous covering, which had been likened to paraffin or waxed paper, oiled silk, parchment, collodion skin, and the appearance of such children, a variety of descriptive terms have been coined and have caused much confusion in both the literature and the textbooks. The clinical appearance is well illustrated by the two cases recorded above which also support the conjecture that there are two separate aetiological groups.

In the first group, known as lamellar desquamation of the newborn, are placed those cases in which the skin is histologically normal and remains so after desquamation has taken place. At birth such infants appear 'varnished' due to a layer of cornified substance resembling collodion. This is usually generalized but may be localized as in the case reported by Finlay and Bound (1952) in which only the feet and hands were affected. The covering cracks and desquamates within a few days or weeks, leaving below the skin which is normal in all respects. The progress of such infants is excellent as their vitality and general health are unimpaired.

The term lamellar exfoliation of the newborn was suggested by Grass and Torok in 1895 and the same year Bowen recorded a further case. He postulated that the membrane was the persistence of a layer of cells of the epidermis distinct from the horny layer and was homologous with the epitrichial layer which covers the hairs of the embryo of certain animals. He also showed that this epitrichial layer usually disappeared about the seventh month of foetal life. Persistence beyond this period causes lamellar desquamation and accounts for the presence of normal skin when this layer is shed. If this assumption is correct it is surprising that the condition is not seen more frequently in premature infants but no such association has been observed. The histological examination of the covering layer confirms, as in Case 1, that it is composed of horny cells and is of epidermal origin. This disproves Kaposi's (1895) suggestion that it is due to an excessive amount and persistence of the vernix caseosa. Thus use of the terms ichthyosis sebacea and sebacorrhoea squamosa neonatorum, which he employed to describe the condition, should be discontinued. Similarly the term, lamellar ichthyosis, as applied by Cockayne (1933) and by Finlay and Bound (1952) to the first group of cases is confusing because collodion skin of the newborn due to lamellar desquamation may be mistaken for, and is to be distinguished from, true ichthyosis which forms the second aetiological group. This congenital disorder of the skin, characterized by a lack of dermal secretions, is associated with dryness and scaliness of the skin, and, in some instances, with warty growths. There is an irregular recessive hereditary tendency.

In its most severe form, the latter disease causes the harlequin foetus. Such a gross abnormality is unmistakable but less severe forms of ichthyosis may present at birth with collodion skin which is to all intent identical with that of lamellar desquamation. After the collodion covering is shed ichthyosis develops afterwards. That redness of the skin is more commonly a feature of ichthyosis than of lamellar desquamation, as suggested by Cockayne (Ellis, 1936), is not borne out by the two cases reported here, both of which had a beefy red skin at first, though bleeding occurred in the creases of the neck and groin in our case of ichthyosis. This is not to be confused with congenital ichthyosiform erythrodermia which may also present at an early age and be familial. In this condition the skin, which is scaly and thickened, is in addition erythematous, while flexural surfaces are particularly involved and



FIGS. 2A and 2B.—Case 2, aged 8 years and 9 months.

here horny excrescences may accumulate. The scalp, which is usually affected, is pink and scaly.

To place a case of collodion skin of the newborn into the correct category, observation for at least the first year of life is required to exclude the chronic ichthyotic condition. In the literature on this subject, however, the majority of case reports lack information on the subsequent progress or of the histology necessary to allocate them to either of these aetiological groups.

Summary

Two further cases of collodion skin of the newborn are recorded. They illustrate the clinical appearance of this condition and two main aetiological groups: (1) Lamellar desquamation in which the skin is subsequently normal, and (2) ichthyosis in which the skin develops the typical changes associated with this disease.

We should like to thank Professor F. M. B. Allen for permission to publish these cases and Dr. J. Martin Beare for his helpful advice.

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CONTROL OF THE BLOOD SUGAR LEVEL IN THE NEONATAL PERIOD

BY

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Hypoglycaemia, as judged by adult standards, has been recorded by the majority of those responsible for approximately 50 papers on the subject of blood sugar levels in newborn infants. Most of these studies may be criticized for one or other of the following reasons. Levels vary not only between individual babies but from day to day in the same infants; this fluctuation is most marked in the first hours of life so that the range of 'normal' from birth on each day thereafter must be found and cannot be determined for the newborn period by considering the values in infants of different ages. The blood sugar has been determined after fasting periods which have been not only of varying length but also shorter than would be acceptable even in a routine laboratory investigation. The chemical method or the way in which it has been employed has been at times unsatisfactory.

Among the well-known investigations are those of Köhler (1932), McKittrick (1940), Norval, Kennedy and Berkson (1949), Reis, De Costa and Allweiss (1950), Pedersen (1952), Creery and Parkinson (1953) and Komrower (1954). Of these the last three publications were concerned only with the first neonatal day, Norval's paper failed to appreciate the changes that might occur in the first hours while Reis *et al.* in an otherwise comprehensive study made no reference to the accuracy of their method. Of those who followed serial levels, Kohler regarded five and a half hours as a satisfactory fasting period, McKittrick accepted a minimum of three and a half, Norval four hours and Reis *et al.* did not mention it.

Previous workers have agreed, however, that individual babies show quite wide fluctuations while there is great variation on any one day in a group accepted as normal. Sugar levels tend to fall for some hours before becoming stabilized and the lowest figures are recorded on the second and third days when a gradual rise is usual. None of the serial studies so far, however, has taken a fast which would be acceptable at any other age, the reason probably being an unwillingness to interfere with the infant's feeding routine.

Economy in blood is essential in small babies and this has led to single specimens only being analysed. Very little contamination or deterioration of reagents introduces quite wide errors and duplicate specimens are therefore more reliable. It is true also that the scrupulous conditions applied to testing a method's accuracy may not always be employed in later use. Wooton and King (1953) have shown how scattered the results on a known glucose solution may be when analysed in different laboratories while Lehmann and Silk (1952) have pointed out the difficulties in colour development and stability when duplicate analyses were made by the method of Folin and Wu or its modifications. King and Garner (1947) have also had difficulty with their modifications of this method while the familiar Folin and Wu tube is a confession of the method's instability. Many of the investigators of neonatal sugar levels have relied, however, on single determinations by this method.

Control of Carbohydrate Metabolism

The elucidation of carbohydrate control in the mature organism is incomplete but the present knowledge of it has been stated by Long (1952) and Talbot, Sobel, McArthur and Crawford (1952). From these reviews of a very great deal of animal and human investigation it is apparent that the sugar-fat-nitrogen hormone (11-17 oxycorticosteroids) plays an important part in maintaining the blood sugar level. From Fig. 1 it may be seen that the sugar-fat-nitrogen hormone accelerates the production of glucose from non-carbohydrate sources (fat and protein) while retarding its oxidation in the tissues. Deficiency of this hormone results in hypoglycaemia, increased tolerance of sugar and sensitivity to insulin, while an increased production leads to directly opposite conditions. The sugar-fat-nitrogen hormone is produced by the adrenal

cortex as a result of stimulation by endogenous corticotrophin (A.C.T.H.) from the anterior pituitary and this accounts for the diabetogenic effects of therapeutic A.C.T.H., for the decreased sugar tolerance in Cushing's syndrome and for the hypoglycaemia of Addison's disease.

Insulin antagonizes the sugar-fat-nitrogen hormone by stimulating glycogenesis and by conversion of glucose into fat and protein. It is now believed that the pancreatic β cells respond not to a pancreatropic pituitary hormone but simply to the blood sugar level and this, should it be raised, may increase insulin production and then exhaust it.

In short, it appears that the homeostatic mechanism by which the blood glucose is maintained at a given level is largely an interplay between the pituitary-adrenal axis and the pancreas, the liver being both fuel reserve and furnace while the hormones form the thermostat (Soskin, 1941).

The Neonatal Adrenal

The adrenal glands of the newborn are much larger in proportion to body weight than at any other age. This is due almost entirely to the large cortex which has a light coloured, narrow exterior and a wide, dark inner zone. Although differentiation into glomerular, fascicular and reticular zones is not so clear as in the adult (Potter, 1952), careful morphological studies led Blackman (1946) to conclude that the foetal cortex corresponded in many ways to the reticular cells of the adult gland and the term 'foetal reticular zone' was proposed. This zone accounts for 85% of the entire neonatal cortex (Swinyard, 1943). Grollman (1936), Reichstein (1936) and Howard (1937) believed it to produce androgenic substances because of its similarity to the zone persisting in the adrenogenital syndrome but Gersh and Grollman (1939) have since failed to demonstrate androgenic activity in the cells while Blackman (1946) did find differences between the reticular zones of normal infants and those with adrenogenitalism.

The foetal cortex is present early in development, becomes increasingly noticeable from the twenty-fifth week of gestation (Clatworthy and Anderson, 1944), and grows immensely towards the termination of pregnancy (Swinyard, 1943).

As unexplained as its development and function is the dramatic involution of the foetal reticular zone which follows immediately upon birth and is independent of maturity so that separation from the mother and the beginning of extra-uterine existence seem to be the only possible causes. Potter (1952) believed that the greatest changes were complete in the neonatal period while McNeill (1947) stated that the foetal cortex had disappeared by the end of the third week. Other phenomena in the newborn, such as enlargement of the breasts, lactation, congestion and enlargement of the external genitals and uterus, involute also with the start of an independent existence, and it seems at least likely that the changes in the adrenal cortex also represent the influence of maternal hormones. If so, then the hormone most likely to affect this gland would be corticotrophin.

O'Donnell, Fajans and Weinbaum (1951) have described the adrenal changes which occur when corticotrophin is given therapeutically. Lipoid is reduced in all zones while there is narrowing of the outer (zona glomerulosa) and hypertrophy of the two inner (zona fasciculata and zona reticulosa) zones. Some of these changes are still visible 23 days after the last dose of corticotrophin but the glands are normal in six months—findings which compare suggestively with the adrenals of newborn infants. The lipoid of the adrenal cortex is believed to be some kind of indicator of its steroid activity (Selye, 1946a; Sayers, Sayers, Fry, White and Long, 1944). Potter records that there is little lipoid in the adrenal cortex at birth and this corresponds to the findings of O'Donnell *et al.* (1951) above after giving corticotrophin. Selye (1946a and b) found that the adrenal lipoid was readily affected by disease and that those who have died of acute disease possessed much less than those who had succumbed to a chronic illness. Very similar observations were made by Sayers and Sayers (1948) while Weltman (1913) in a group described as the 'hyperacutely dead' found plenty of lipoid substance.

The fact is that any newborn who has died has already suffered stress sufficient to change the lipoid content of the cortex while the enormous adaptation required to establish extra-uterine existence must make a great call on the adrenals. Histological examination bears no relationship necessarily to their normal function in the newborn for, short of infanticide, there is no way of securing a normal gland. Because of this, studies should be made rather of adrenal cortical function in normal and abnormal live infants.

The fact that operative procedures, cold, haemorrhage and other stimuli result in eosinopenia has been recognized for some time and Selye (1949) included this as part of the alarm reaction. Hills, Forsham and Finch (1948) demonstrated that corticotrophin and compound F produced a decrease in the numbers of circulating eosinophils and have shown that the stimuli required to reproduce it are stress conditions, while Thorn, Forsham, Prunty and Hills (1948) made it clear that the adrenal cortex was essential if eosinolysis was to occur and that the sugar-fat-nitrogen hormone was responsible for it

TABLE 1
EOSINOPHIL RANGE IN NORMAL NEWBORN INFANTS

	Day 1	Day 2	Days 3–5	Days 6–8	Days 8–10	Days 9–11
Forkner (1929)	0–895 (429)		168–1,110 (600)	160–727 (411)		205–873 (417)
Klein and Hanson (1950)	78–988 (359±47)	75–1,100 (420±43)			63–483 (268±42)	

Mean values in brackets.

(Fig. 1). Several studies of the numbers of circulating eosinophils in newborn infants have been made (Table 1). When considering the means of the ranges given it appears from both series that the values rise in the first few days of life and then progressively fall although it must be acknowledged that the scatter is so wide that the significance of the mean is doubtful. The values are, however, above the mean for adults. Burrell (1953) recorded graphically the mean of eosinophil counts in full-term infants as rising from birth to 1 week and becoming stabilized at that point.

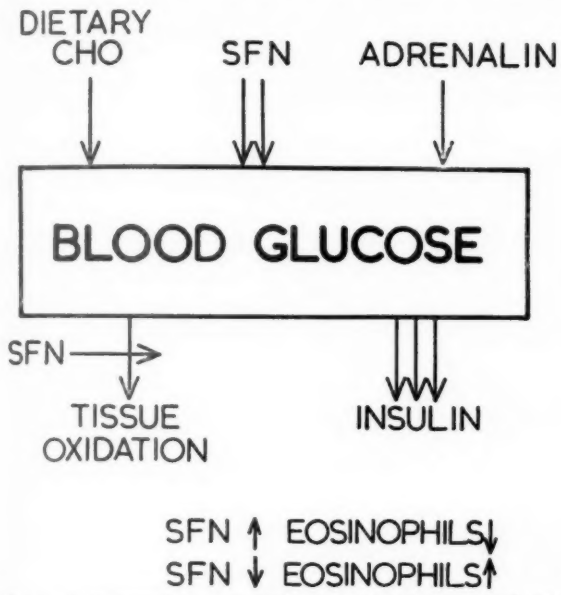

FIG. 1.—Diagrammatic representation of carbohydrate control (after Talbot).

Svensgaard (1931-32) showed glucose tolerance to be greater in the first few days than in the second week. Day (1948) studied the 11-17 oxycorticosteroids in the urine of newborn infants and found little to suggest significant deficiency, but Venning (1950), assessing the response of the newborn adrenals to corticotrophin by measuring eosinopenia, 17-ketosteroids and 11-17 oxycorticosteroids, found that the glands of 2-day-old infants were less responsive than those of 9-day-olds. This was substantiated independently by Klein (1950, 1951).

Talbot, Zygmuntowicz, Wood and Christo (1950) reported, too, that corticoid excretion per unit of body surface was constant throughout life except in the first few days when it was low. Klein, Fortunato and Papadotos (1954) have shown by direct estimation of blood corticoids that these are

TABLE 2
SERIAL READINGS OF PARALLEL BLOOD SUGAR AND EOSINOPHIL LEVELS IN NORMAL FULL-TERM NEWBORN INFANTS

Age	Blood Sugar (mg. %)						Eosinophils (cells/c.mm.)					
Hours	No. of Observations	Arithmetic Mean	Range Min.	Range Max.	Standard Deviation	Coefficient of Variation (%)	No. of Observations	Arithmetic Mean	Range Min.	Range Max.	Standard Deviation	Coefficient of Variation (%)
Birth	30	75·5	43·0	104·75	14·41	19·1	32	451	70	1,153	287·6	63·8
½	31	76·6	44·0	127·5	19·38	25·3	—	—	—	—	—	—
1	31	71·0	39·0	121·0	20·57	29·0	—	—	—	—	—	—
2	32	64·3	39·0	102·5	13·76	21·4	—	—	—	—	—	—
3	—	—	—	—	—	—	30	304	86	850	194·7	64·0
4	32	63·2	31·0	87·0	11·01	17·4	—	—	—	—	—	—
6	31	63·1	38·5	90·0	11·27	17·9	32	331	33	794	216·5	65·4
Days												
2	32	65·6	42·75	102·0	12·00	18·3	32	365	47	966	199·5	57·7
3	32	64·8	45·5	90·75	11·02	17·0	31	390	116	882	180·2	46·2
4	32	69·1	42·0	89·25	10·86	15·7	32	289	18	1,076	184·6	64·0
5	32	73·3	49·25	95·5	11·49	15·7	32	262	30	719	162·9	62·2
6	32	74·3	51·25	94·25	10·20	13·7	32	273	36	705	152·6	55·8
7	31	77·5	55·0	104·75	10·04	13·0	32	273	78	561	109·3	40·0
8	31	78·7	54·0	114·25	13·34	16·9	31	275	83	550	127·6	46·4
9	30	82·7	60·75	111·0	12·26	14·8	30	271	53	570	124·8	46·1
10	28	81·3	60·75	98·0	9·37	11·5	29	259	116	494	105·5	40·8

deficient in the immediate newborn period and probably normal by the second week.

So far, then, as functional studies of the adrenal cortex have gone at this age they suggest that after birth there is a period of relative adrenal hypofunction. In view of this and the known part played by the sugar-fat-nitrogen hormone in maintaining the blood glucose level it is of interest that this period corresponds to that on which lowest glucose levels exist.

The Present Investigation

This study was made to determine whether serial parallel investigations of glucose and eosinophil levels in capillary blood showed simultaneous movement in opposite directions which might suggest from the above argument that each was associated with the adrenocortical changes.

The infants studied were born spontaneously after normal pregnancy, pethidine and gas and air being the only analgesics. All were over 5½ lb. birth weight and breathed within two minutes. Their course in hospital was uncomplicated and no congenital abnormalities were present.

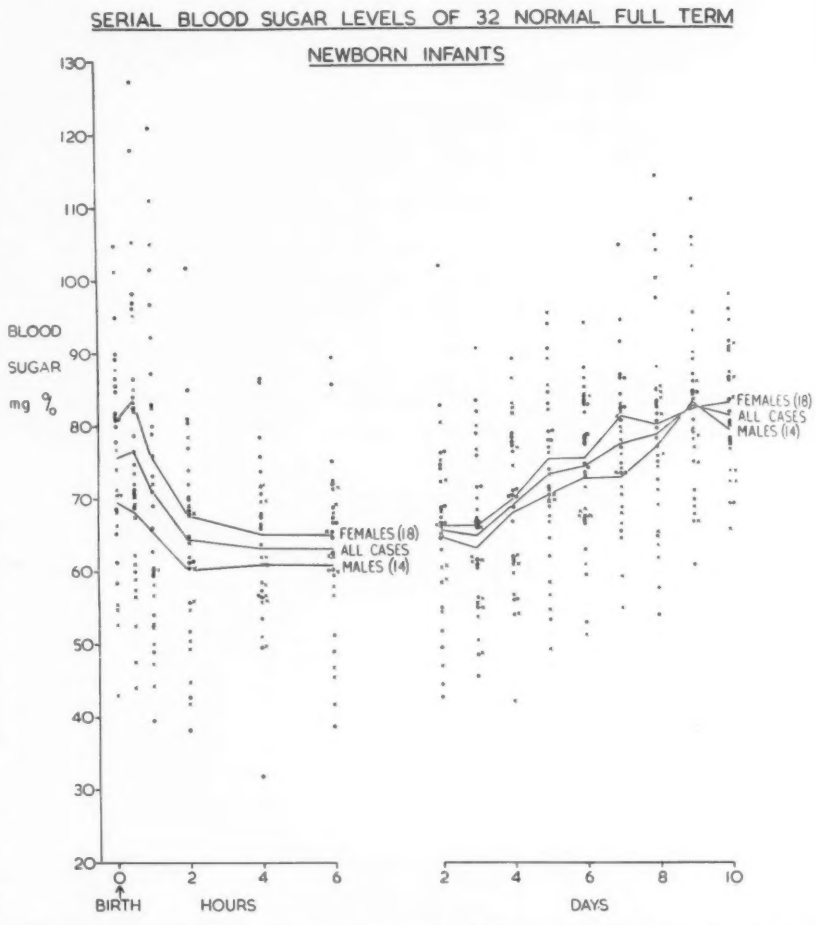

FIG. 2.—Time-trend diagram for blood sugar levels of 32 normal full-term newborn infants showing scatter on each day.

All specimens were taken personally at 5.30 a.m. in order to avoid disturbing the feeding routine which would have been occasioned had specimens been taken later. The infants had fasted eight hours. Glucose determinations were made personally in duplicate by the method of Ramsay (1950). The method has the advantage to the paediatrician that duplicate analyses may be made on 0·1 ml. (as in this investigation) although the method is sufficiently sensitive to allow a single estimation on 0·02 ml. of blood. The method is straightforward and the final colour is stable provided it is shielded from sunlight. Errors, however, are readily introduced by contamination of apparatus and cleaning must be scrupulous.

In this study, the accuracy of the method was tested before beginning the investigation, and was found to be extremely good. Three sets of 12 readings (six duplicate analyses) at various known concentrations of glucose were analysed; the result gave a very small scatter even in the very dilute solution (25 mg. %). The highest scatter in any set of 12 gave a standard deviation of only 1·8% of the mean. The same standard of accuracy was maintained throughout the investigation, frequent checks being made against glucose standards, and duplicate analyses of the blood specimens were made throughout in order to reduce possible error. Occasionally specimens were lost due to breakage or error while toward the tenth day some cases were lost from the series owing to premature discharge from hospital.

The blood sugar was determined at birth, half-hourly until two hours and then two hourly till six hours. Thereafter it was determined daily until the tenth day.

The eosinophils were counted using the technique modified by Smart (1950) from Randolph's method (McArthur, Smart, MacLachlan, Terry, Harting,

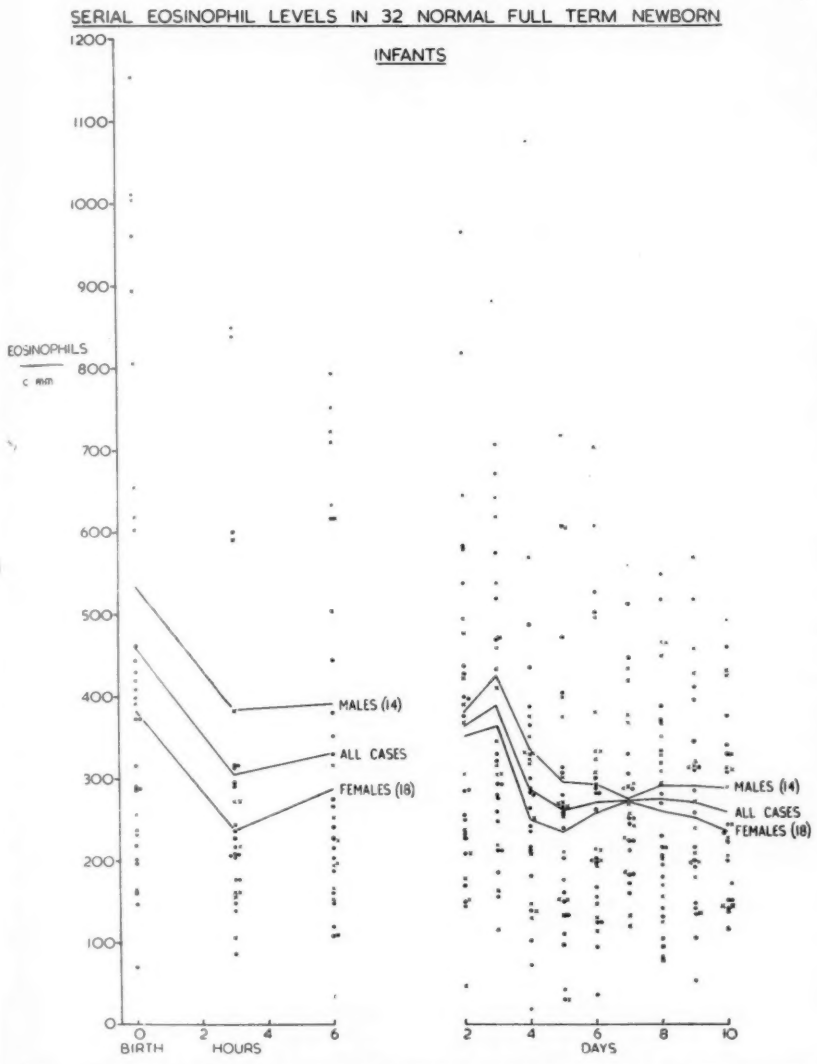

FIG. 3.—Time-trend diagram for eosinophils levels in 32 full-term, newborn infants showing scatter on each day.

Gautier, Godley, Swallow, Simeone, Zygmuntowicz, Christo, Crepeaux, Point and Benson (1954). The diluent consisted of equal parts of an 0·05% aqueous solution of phloxine and of propylene glycol. Blood was taken in one pipette and was carefully mixed; the total number of cells in four Fuchs-Rosenthal chambers was counted.

Results

Of the 32 infants in the series 18 chanced to be females. The blood sugar and eosinophil readings were submitted to statistical analysis not only of average figures for each feature but also of the concomitant trend of the two features in each individual child; this was done not only for the actual readings at each age but for the day-to-day changes in readings throughout the study. The methods of analysis are described in the Appendix.

The Group Described Collectively

At Each Day. The average values for blood sugar readings and eosinophil counts were studied in various ways. The standard deviations and coefficients of variation were calculated for each feature for each time unit (Table 2).

Taking the immediate birth period first it may be seen from the time-trend diagrams (Figs. 2 and 3) and from Table 2 that the mean blood sugar level for the group as a whole fell rapidly during the first two hours of life and that this was arrested before a similar period of time had elapsed: that is, the average blood sugar for the group fell by 11·2 mg. in the first two hours, by 1·1 mg. in the following two hours and by 0·1 mg. only in the next two hours. Similarly in the group as a whole the mean of circulating eosinophils fell by 156 during the first three hours of life and then rose by 27 cells/c.mm. in the next three hours, a considerably smaller increase.

In the next period, from the second to tenth days, the mean blood sugar level for the group as a whole increased steadily from 65·5 mg. % on the second to 82·7 mg. % on the ninth and 81·3 mg. % on the tenth day. Over the same period the group average value of the eosinophil levels decreased from 390 cells/c.mm. on the third day to 259 cells/c.mm. on the tenth but this fall took place largely from day three to four.

Mean values cannot be taken as adequate descriptions and in this series particularly the scatter of values around the group mean at any time unit for both blood sugars and eosinophils was great. This can be seen both from the time-trend diagrams, which illustrate also the daily scatter of the actual

observations, and from the coefficients of variation in Table 2. In the blood sugar the coefficient of variation (=S.D./mean expressed as a percentage) rose from 19% to 29% in the first hour and settled with some fluctuations thereafter to 12%. This is a high coefficient of variation. For eosinophils the scatter of values around the group mean was very much greater, the coefficient of variation starting above 60% and fluctuating widely above 40% even towards the tenth day.

Day-to-day Mean Increments. Although the scatter of actual values on individual days decreased slightly, suggesting stabilization, the actual scatter of increments of individual infants from day to day did not decrease.

Components of the Group

Time-units. Although the group mean for blood sugar tended to rise daily from the third day and over the same interval the group mean for eosinophils tended to fall; this was not accepted as reflecting the behaviour of individuals within the group. So great was the daily scatter of readings, particularly for eosinophil values, that more detailed analysis of this behaviour was considered essential, for many individuals within the group could have had rising eosinophils even though the group mean fell slightly.

The component 'paired readings' of blood sugar and eosinophil counts for each child at each time unit to some extent explain this wide scatter. The relationship existing between the blood sugar and eosinophils for each infant on each day was found from the correlations (see Appendix) and is also illustrated in the scatter diagrams (e.g., day 3, Fig. 4, and day 6, Fig. 5).

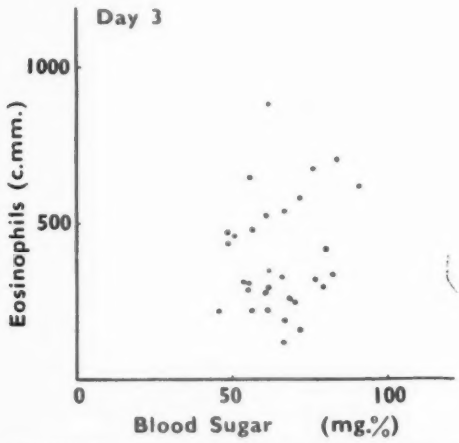

FIG. 4.—Scatter diagram of eosinophils against blood sugar values on day 3.

It is clear from these that the eosinophil levels were not lower in those infants who had higher blood sugars. On some days the visual impression appears to indicate that those infants with higher sugar values tended to have higher eosinophil levels. On most days even this visual impression is absent.

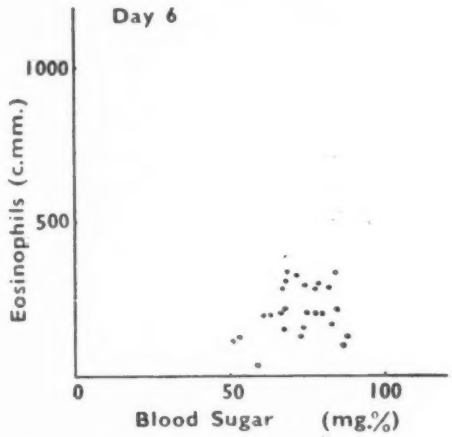

FIG. 5.—Scatter diagram of eosinophils against blood sugar values on day 6.

Increments. The calculation of the correlation coefficients in fact shows that there was no relationship whatever between the changes in blood sugar and the changes in eosinophils; on some days there was a small positive correlation and on others a negative, as detailed in the Appendix.

The Individual Child

Though there was no relationship between the two features on any day or between one day and the next, it might still be possible for each child to have falling eosinophils and rising blood sugars, each having its own cycle, and the phase in any individual not necessarily corresponding in time with the same phase in another individual. Graphs were therefore drawn for each individual showing the changes in both features. It then became apparent that the following patterns of movement existed for individuals within the group: A, blood sugar and eosinophil movement fairly consistently in opposite directions (Fig. 6); B, an upward trend for both blood sugar and eosinophils (Fig. 7); C, level blood sugar trend and downward trend for eosinophils (Fig. 8); D, no eosinophil trend while blood sugars increased (Fig. 9); E, blood sugar increased, eosinophils decreased but not simultaneously or consistently in opposite directions (Fig. 10).

In five individuals of the 32 in the group, the

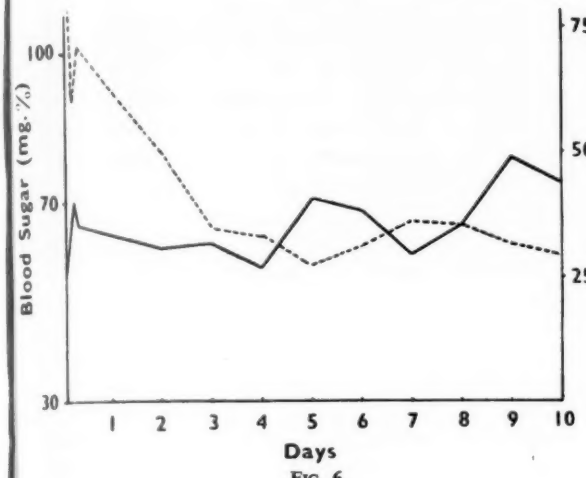

FIG. 6.

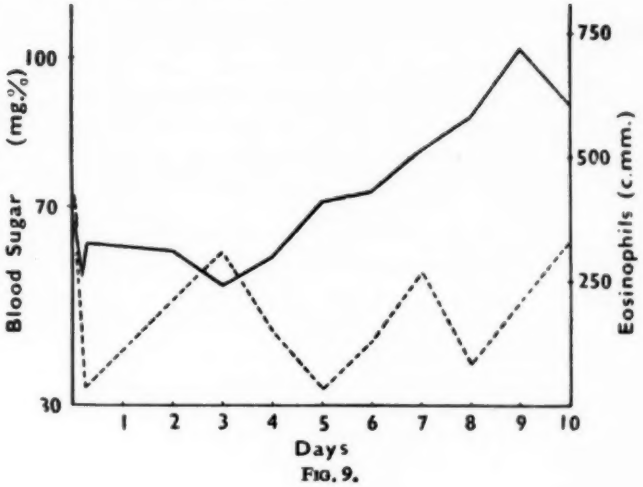

FIG. 9.

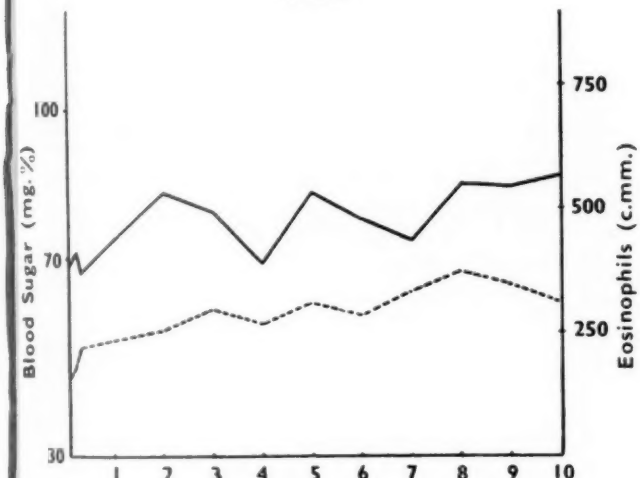

FIG. 7.

FIGS. 6-10.—Patterns of blood sugar and eosinophil movement. Unbroken line represents blood sugar value. Broken line represents eosinophil count.

FIG. 6.—Pattern A. Fairly consistently in opposite directions.

FIG. 7.—Pattern B. Upward trend for both blood sugar and eosinophils.

FIG. 8.—Pattern C. Blood sugar trend level, eosinophil trend downwards.

FIG. 9.—Pattern D. Blood sugar increases, no eosinophil trend.

FIG. 10.—Pattern E. Blood sugar increases, eosinophil count decreases; movement not consistently in opposite directions.

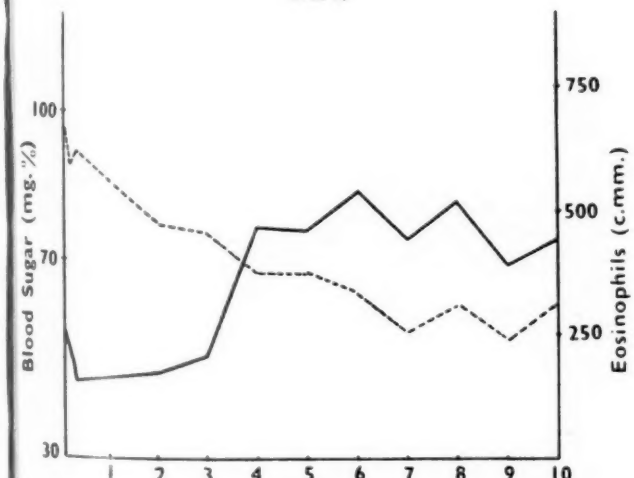

FIG. 8.

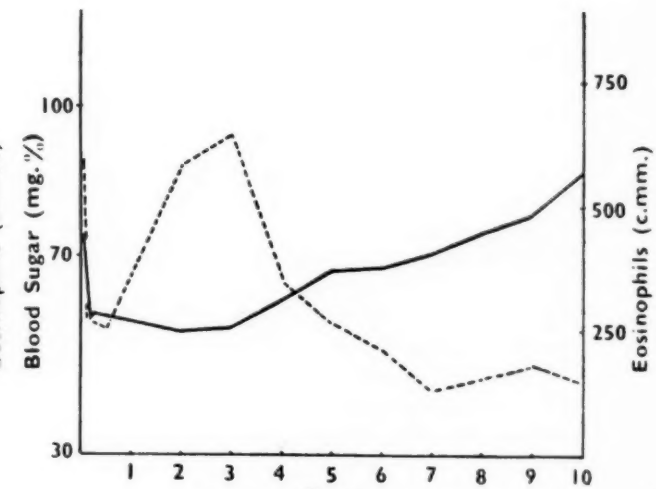

FIG. 10.

day-to-day graphs of the two features formed a pattern of opposite movement of type A, in nine both features rose as in B, in two the blood sugar was level and the eosinophils decreased as in C, in 11 there was no trend for eosinophils although the blood sugars increased as in D, and in five the blood sugars increased and the eosinophils decreased as in E.

Five infants only of the 32 studied produced a pattern of simultaneous movement in opposite directions. The largest single group of individuals, 11, had widely varying eosinophil levels from day to day which conformed to no pattern at all but were associated with rising blood sugar values. The majority of infants showed an upward trend of blood sugars, and, although the eosinophil pattern was more erratic, six infants had particularly high levels at birth and another five such very high levels on the third day that they dominated the means. This helps to explain why a study of the means alone gives the impression of increasing blood sugar and decreasing eosinophils.

It is clear from this individual analysis that simultaneous movement in opposite directions did not often occur.

Discussion

A number of theories, mostly relating to the function of the liver, have been elaborated to explain the hypoglycaemia of newborn infants and these have been reviewed by Smith (1951) and by Pedersen (1952). van Creveld (1929), investigating the blood glucose levels of premature infants, suggested that hepatic immaturity was responsible, for with progressive maturation the levels rise. That the liver is immature in its function in both premature and in the majority of full-term infants has been shown in a variety of ways and more recently by Mollison (1948) but why it should be responsible for hypoglycaemia is far from plain. It is true that the lowest post-natal levels correspond roughly to the days of weight loss and of minimal calorie intake but the newborn infant is born with an adequate glycogen store in the liver which is built up during the last trimester (Windle, 1940). This means that the low blood sugar levels are not due initially to lack of glycogen as suggested by van Creveld (1929) when he spoke of glucose from the placenta by-passing the foetal liver via the ductus venosus. Ward (1953) suggested that the glycogen was used quite quickly in starvation, but the cases studied were few and the duration of pregnancy and birth weights very varied.

There is no question of adrenalin deficiency in newborn babies (West, Shepherd, Hunter and MacGregor, 1953) and although it has been suggested that because of hepatic immaturity glycogenolysis does not result from adrenalin secretion the work of Desmond, Hild and Gast (1950) has shown that the sugar level does rise when adrenalin is injected at any time from birth although it is true that flatter curves occur in the first few days than later.

The possibility of the foetal pancreas producing an excess amount of insulin has been raised and there is controversy as to whether or not functional over-activity exists. Nakamura (1924) described an excess of islet cells in foetuses and newborn infants, while Fisher and Scott (1934) found pancreatic insulin levels in the newborn calf higher than in the adult animal. Köhler (1932) and Ketteringham and Austin (1939) applied this to human infants and ascribed the hypoglycaemic levels to true insulin hypersecretion.

Winter (1933) opposed the suggestion of excessive insulin on the grounds that the post-natal blood sugar was rising at a time when the pancreas was unchanged but this assumes that the function of a normal endocrine gland is necessarily reflected in the histology of those who die. White (1949) discarded the idea of hyperinsulinism as the mechanism of hypoglycaemia in the infants of diabetics because in her view such a process should inevitably be continuous and should eventually produce a zero value. Such an argument would also apply to the normal were hyperinsulinism a fact and were no other mechanism to intervene. Hartmann and Jaudon (1937) believed the cause to be relative hyperinsulinism, without necessarily hyperplastic β cells, there being incomplete development of opposing mechanisms; while Wachter (1949) speaks of an absolute hypersensitivity to insulin in the first few days of life. The latter found that adrenalin was capable of producing a normal rise at this age, but if insulin were previously injected then no such rise occurred, a phenomenon confined to this age group. No explanation of the hypersensitivity was offered.

Soskin (1941) and Soskin and Levine (1946) believed the fasting blood sugar at any age to be identical with the hepatic threshold for glucose; above the threshold liver glycogenesis occurs and below it there is liver glycogenolysis. The hepatic threshold in turn is determined by hormonal activity, insulin lowering it and anterior pituitary hormone producing a rise. Pedersen (1952) believed the blood glucose level on the first day of life in normal infants and in the offspring of diabetic women to be explicable on this basis. The foetal level *in utero* is thus determined by the maternal and in turn dictates the foetal output of insulin. The

latter is responsible for the foetal liver threshold so that the higher the maternal level the lower the foetal threshold and the more profound the glucose levels in the first 24 hours. Similarly low maternal levels result in a low foetal output of insulin, a high foetal liver threshold and higher levels on the first day of extra-uterine existence.

Such a theory has much to commend it but takes no cognizance of the pituitary-adrenal axis which plays such a big part in carbohydrate metabolism and which varies so much at this age.

The stress of pregnancy does seem to result in increased activity in the maternal pituitary and adrenal glands, particularly in the latter weeks, and the cortisone output in the maternal urine from the eighth month is raised, the range in normal pregnancy being the same as that found in cases of medical stress (Cope, Boysen and McCrae, 1951). Similar results were previously found by Venning (1945).

The following hypothesis was elaborated from a study of the literature, and the investigations described in this paper were undertaken to shed light upon it. The increased maternal corticotrophin crosses the placenta, stimulates the infant's adrenals, produces the well-known foetal reticular zone and, with placental diffusion of glucose, the foetal liver threshold is set high. The upward trend of foetal blood glucose stimulates the pancreas so that the production of insulin may indeed exceed that existing in later life.

When the cord is clamped, the maternal source of sugar supply is no longer available and foetal glucose levels begin to fall, insulin producing hepatic glycogenesis. It is possible that the increasing output of maternal corticotrophin in labour results in some spill-over to the foetus; but the great physiological stress of adaptation to extra-uterine life, with its problems of respiration and thermal independence, provides stimulation for the endogenous production of corticotrophin, and this in turn results in secretion of the sugar-fat-nitrogen hormone. Resulting economy in tissue oxidation and gluconeogenesis with the diminishing stimulation to insulin production and possibly release of the hormone of the adrenal medulla account for the arrest of the falling blood sugar values. In some cases the pituitary-adrenal axis may be stimulated by stress before birth, as in asphyxia, and may be present at birth with raised or rising sugar values (Miller, 1941) in the alarm hyperglycaemia described by Selye (1946a). Following this maximal effort in the normal infant there may be a slight further fall until about the third day. This would be consistent with the description by Selye (1946b) of blood sugar changes in animals exposed to stress in which there is a rise in the shock phase followed however by a fall and then a progressive rise in the stage of 'countershock'. The newborn infant differs from the experimental animal in that production of insulin may be above normal. Following the third day the pituitary adrenal axis is firmly established, eosinophils begin to fall again, corticoid excretion increases, there is consequently a progressive rise in the hepatic threshold and a parallel rise in the fasting blood sugar level.

Somewhat similar possibilities occurred to Klein and Hanson (1950) who considered that lack of corticotrophin in the infant might be related to neonatal hypoglycaemia, and to Talbot *et al.* (1952) who, discussing low corticoid excretion in the first week of life, state:

> 'It remains to be determined whether the tendency of infants to have relative eosinophilia, to develop hypoglycaemia and to show involution of the foetal zone of their adrenal cortices during the neonatal period, is significantly related to the foregoing.'

It was hoped that confirmation of the above hypothesis might have been obtained from the present study. But statistical analysis has shown that the trend of the group averages, which might have been misconstrued as confirmatory, was of no use whatsoever in depicting individual trends; and other methods of examination of the values have also shown that no simultaneous movement in opposite directions occurred.

The eosinophil count, however, is no substitute for direct estimation of 11-17 oxycorticosteroids; and it is felt that the experiment may have failed to prove, or entirely to disprove, its point because of the weakness of this method of estimating adrenocortical function. When serial estimations of sugar-fat-nitrogen levels are possible in small infants they may throw further light on the relationship between changes in the neonatal adrenal and the chemical hypoglycaemia.

Summary and Conclusions

The present knowledge of carbohydrate control, of the neonatal adrenal, and of hypoglycaemia in the newborn is briefly reviewed, and an attempt made to link the latter with the anatomical and functional changes in the adrenal gland at this age. Evidence in favour of such a linkage would have been obtained had it been possible to show that simultaneous movement of blood sugar levels and eosinophil counts in normal newborn infants occurred in opposite directions.

Serial studies of blood sugar levels and eosinophil counts were carried out in a group of 32 normal infants.

Previous work on the neonatal blood sugar levels is open to some criticism but it was confirmed that the variation between individuals at any time unit was wide and also that considerable variation occurred in individual infants at each time interval.

This scatter of individual values at any time unit was so great as to render the arithmetic mean of the group valueless as representing the behaviour of individuals.

The blood sugar level tended to fall fairly rapidly in the first hours after birth but was stabilized by about four hours. It remained as an impression that those individuals in whom the blood sugar rose immediately after birth were those who approached more closely to the two minutes accepted as the upper limit of normal before respiration was established.

An upward trend in blood sugar values over the 10-day period occurred in the majority.

From scatter diagrams, not reproduced here, there was no correlation between body weight and the blood sugar level.

The eosinophil levels of the group were appreciably higher than in adults.

The scatter of eosinophil counts between individuals was great at any time unit and also in the same individual at any time interval. As with blood sugar this scatter was sufficiently great to invalidate the group mean as a representation of individual behaviour.

Twenty-six of the infants showed a fall in eosinophils, many of them a substantial fall, in the first few hours.

The relationship between the blood sugar level and eosinophil count was studied in individual cases and five distinct patterns found. These showed that the pattern of inverse movement of the means of the two features was false. The mean blood sugar level rose steadily from the third to the tenth day whereas the fall in the mean eosinophil level took place largely between the third and fourth day. Comparison of the change in mean values was therefore impossible over the same time interval.

When the behaviour of individuals was studied it was clear that simultaneous movement of blood sugar values and eosinophil counts in opposite directions did not take place but it remains possible that direct measurement of the sugar-fat-nitrogen hormone production would show a relationship between a period of adrenocortical hypofunction and hypoglycaemia.

I wish to record my gratitude to Professor R. W. B. Ellis for his encouragement and advice and for permission to work in the nurseries under his care; to Dr. E. C. Fahmy and Professor R. J. Keller for permission to work in their units and to the latter for generous laboratory facilities; to Professor G. F. Marrian and Dr. W. N. M. Ramsay for advice on biochemical methods and other matters; to the nursing staff of the Simpson Memorial Maternity Pavilion for their cooperation and to my wife whose assistance made the investigation possible. The work was carried out during the tenure of the George Guthrie Research Fellowship of the University of Edinburgh.

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APPENDIX

SUMMARY OF STATISTICAL METHOD

BY

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The analyses of the serial observations of blood sugars and eosinophils were directed first to the description of the levels found in these newborn infants in order to establish a standard with which other infants might be compared, and secondly to the examination of the hypothesis that in the newborn infant the change in blood sugar is synchronous with but, in the opposite direction to, the change in circulating eosinophils. Descriptions consisted of means, standard deviations from means, coefficients of variation and sampling errors of means, for males and females separately as well as for the group as a whole. In addition, correlation coefficients between blood sugar and eosinophil levels in the same infant were calculated for each age, and also for the day-to-day changes from the first day to the tenth and for the change between levels in the interval sixth to tenth day.

Group Descriptions at Each Age

Blood Sugar Levels at Each Age. The variability of the readings around the mean was considerable at each age, and there was little regularity either for males or for females; even at the later ages, the range of normality was from 30% to 50% higher or lower than the mean. There was no significant difference between the sexes; the slightly higher blood sugar means for females than for males were well within the range of chance occurrence. The sampling errors of the means were too high to define the mean as a reliable index for the group. The results indicated that the means could not be taken as definite standards either for the purpose of defining normal children or for the purpose of comparison with other groups of infants. It appeared that blood sugar in the individual infant was too variable a character to constitute a satisfactory index of adrenal function during the first 10 days of life.

Circulating Eosinophils at Each Age. The impression of a falling trend in the group mean was not confirmed by the trends of the male and female means separately; for males alone the means tended to rise in the later days. However, standard deviations and sampling errors of means were so great that no precise trend in eosinophil levels in the individual could be deduced, and the normal range on any day could have been from zero to more than double the mean. The differences between male and female means were not significant. The tremendous fluctuations in daily eosinophil levels in each child indicate that this character cannot be used as an index of the infant's functional response in the first 10 days of life, and that the group means cannot be taken as definite standards for purposes of comparison.

Day-to-Day Changes. It has already been noted that, although after the third day the group means of blood sugar and eosinophil levels appeared to move steadily, the means for males and females separately did not show any consistent day-to-day trend. The explanation of this apparent inconsistency can be found in the standard deviations of the individual increments, which were so great that, during each time-interval, large decreases in blood sugars were just as much within the range of normality as large increases. The scatter of the day-to-day increments was even greater for eosinophils than for blood sugar.

This variability in changes from one day to the next might be thought to conceal a steady trend which would emerge if a longer interval were studied. However, for the four-day period from the sixth to the tenth day the variability was just as apparent (Fig. 11); both for blood sugar and for eosinophils large decreases and increases fell within the normal range. These results indicate that the means of day-to-day changes cannot be taken as definite standards for the purpose of defining normal children or for the prediction of expectation in the trend of blood sugar or eosinophil levels.

Group Components: Correlation between Blood Sugar and Eosinophils

It is often assumed that the time-trend of a group mean can be taken as representing also the time-trend in the individual. That this is not justified when the character is very widely scattered in the population has already been illustrated above; for the purpose of treating an infant and for prediction for the individual it is necessary to

know the extent of correlation between the two characters in the individual child. In the present series of newborn infants, the correlations between blood sugar and

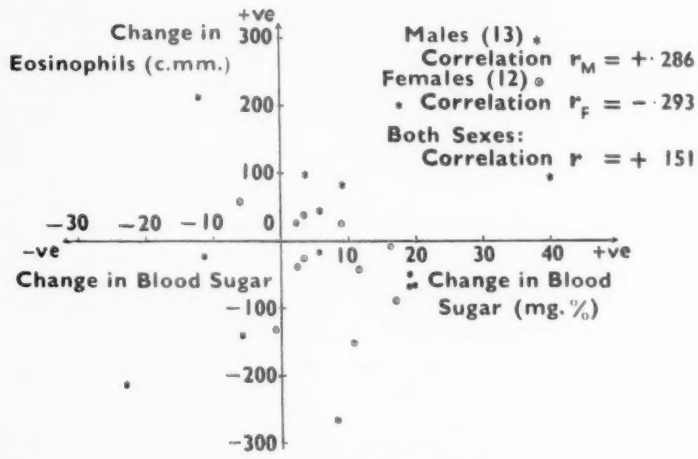

FIG. 11.—Graph showing blood sugar change against eosinophil change for the period day 6 to day 10.

eosinophil levels were not significant, being mostly extremely small. Moreover, most of the coefficients were positive—whereas, if there had been an inverse relationship of high blood sugar to low eosinophil levels, one would expect to get negative correlations fairly consistently. The few negative correlations which occurred in one sex were on days when for the other sex the correlation was positive. The conclusion must be that there was no consistent relationship between the levels of blood sugar and eosinophils in the individual infant on any day up to the tenth.

It might be thought that, nevertheless, the direction of change in blood sugars was inversely related to the direction of eosinophil change. From the correlation coefficients between blood sugar and eosinophil day-to-day changes, it was evident that there was in fact no relationship whatever. Many of the correlations were positive though not significant, and the negative correlations which did occur were quite insignificant. Over the four-day period, when trends in individual infants might have become more stable, the correlation between blood sugar increases and eosinophil increases was actually positive for the group taken as a whole, though it was negative for the females taken alone. This can be seen in Fig. 11, in which is illustrated the individual infant's blood-sugar change against his or her eosinophil change. During this four-day interval, four males and seven females had an increase in blood sugar accompanied by a decrease in eosinophils, and one male and one female had a decrease in blood sugar accompanied by an increase in eosinophils. On the other hand, five males and three females had an increase in both characters, whilst three males and one female had a decrease in both. Thus it appears that, even over a longer period than one day, no relationship could be found between blood sugar and eosinophil trends during the first ten days of life.

Conclusion

The very detailed analyses of the serial readings of blood sugars and eosinophils, both for daily levels and for day-to-day changes, were undertaken in order to scrutinize most closely the hypothesis that in a newborn baby (after the first few hours) there would be a rise in blood sugar and a fall in eosinophils. No such relationship was found. This failure may well be due to the unreliable index represented by the circulating eosinophils, whose day-to-day fluctuations have been shown to be so great that their mean values have little meaning. These statistical findings do not prove that the hypothesis is mistaken; we state only that we have been unable to find any evidence in its support.

FIVE CASES OF ACUTE INFECTIVE POLYNEURITIS (GUILLAIN-BARRÉ SYNDROME) IN CHILDREN

BY

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(RECEIVED FOR PUBLICATION MAY 13, 1954)

Guillain, Barré and Strohl (1916) described a syndrome which they believed to be new. Their findings were based on the study of two soldiers complaining of abnormal sensations in the feet, followed by weakness of the legs and difficulty in walking. Later the legs and then the arms became paralysed. In neither patient was there preceding illness or fever and both made a complete recovery. Lumbar puncture produced a cerebrospinal fluid with normal pressure and cell count but containing increased protein, in one case 250 mg. and in the other 85 mg. per 100 ml.

Similar cases were also described in England by Holmes (1917) and by Bradford, Bashford and Wilson (1918). They did not, however, give cerebrospinal fluid protein levels. The latter workers claimed to have produced a similar disease in monkeys by subdural inoculation of material from fatal cases. The condition came to be known in English writings as acute infective polyneuritis, although the infective nature was never confirmed experimentally by later workers.

The first reported case of the syndrome in a child was that of Monnier-Vinard (1925). Taylor and McDonald (1932) described 16 cases of which two were in children. Ansay (1937) stated that the syndrome was rare in children and reported a case in a boy of 8½ years. Van Bogaert, Philips, Radermecker and Verschraegen (1938) reported a small epidemic of cases of which six were in children. Debré and Thieffry (1951) discussed the features of 32 personal cases in children and thought that the frequency and clinical picture of the condition in childhood were insufficiently recognized.

The disease in childhood seems to have been little described in the English literature, although there are papers in American, French and other journals. Petch (1949) described eight cases of which one was in a child.

Case Reports

Case 1.—A girl aged 16 months was admitted on January 9, 1952, with a history of being miserable and unwell for 16 days. At first she had wanted to be nursed and was happier when off her feet. Seven days before admission she began to hold on to objects in walking and tended to fall over. Then she cried when her legs were touched and gradually 'lost the strength of them'. At times she had seemed febrile. There was no vomiting, no past history of ingesting any toxic substance, nor of mumps or any other illness. She had not been immunized against diphtheria. There was no history of a tubercular contact. Previously she had walked well.

On examination the temperature was 101°; she was unable to sit or stand, but seemed mentally lucid. There was slight coryza and cough. Examination of any part of the body provoked screaming; there appeared to be generalized tenderness which included the neck muscles. The neck was slightly stiff and Kernig's sign was doubtfully positive. There was no evidence of weakness of the motor cranial nerves and the fundi appeared normal. In the upper limbs power and tone were normal and tendon jerks were present. The abdominal reflexes were obtained. Both lower limbs were weak and flaccid in all muscle groups, proximal as well as distal. Some active movement was still present. There was no muscular wasting. Knee and ankle jerks were absent. Sensation was difficult to assess but the patient appeared to feel a pinprick. Except for a few rhonchi in the chest, no abnormalities were found in other systems.

INVESTIGATIONS.—Lumbar puncture gave clear cerebrospinal fluid with a pressure of 140 to 180 mm. of water; cells, 2 per c.mm.; protein, 85 mg. per 100 ml.; Pandy's test for globulin, positive; sugar, 63 mg. per 100 ml.; chlorides, 710 mg. per 100 ml. The Wassermann reaction was negative, as was culture for tubercle bacilli. Haemoglobin was 64% (9·5 g. per 100 ml.), and a white blood count gave 11,800 per c.mm. (polymorphs 60%, lymphocytes 28%, monocytes 11%, eosinophils 1%).

A blood culture showed no growth. The Mantoux test was negative down to 1 in 100.

No porphyrins were detected in the urine. The Paul Bunnell test was negative.

No abnormality was seen in a radiograph of the spine, but doubtful miliary spots not eventually confirmed in further films were seen in a radiograph of the chest.

The Schick test was positive.

Owing to the doubtful *x*-ray findings, intramuscular streptomycin was started in doses of 0·5 g. daily, together with *para*-aminosalicylic acid, 9 g. daily, continued for

seven days, also streptomycin, 20 mg. intrathecally on three successive days. The cells in the cerebrospinal fluid then rose to 800 per c.mm. on one occasion. This was probably a toxic effect of streptomycin.

In the first week after admission the child was noticed to have slight difficulty in swallowing solid food. She did not choke or regurgitate food through the nose. During the first two weeks weakness of the lower limbs increased until there was scarcely any voluntary movement. The muscles continued to be tender. For three weeks there was occasional slight pyrexia with one rise to 102° associated with cough and rhonchi in the chest on the sixteenth day.

In the third week, slight improvement in power and tone of the lower limbs was evident. Improvement was maintained; in the fifth week the patient could kneel and in the seventh week sit unsupported, stand, or walk holding on to the cot sides. In the tenth week she was able to walk unaided and was discharged in good health with power and tone almost normal. Throughout the illness there was no muscular wasting. She had physiotherapy consisting of assisted active movements and walking lessons. The electrical reactions of the muscles were not done.

When seen two months later she appeared healthy and walked well, apart from slight hyper-extension of the left knee and a valgus left ankle. The knee and ankle jerks remained absent.

Case 2.—A boy aged 3 years was admitted on July 27, 1949, with a history of tonsillitis three weeks before, associated with pain and 'stiffness' in both legs, more marked in the left. In the first two days of the illness he had been febrile. The temperature then remained normal. Two weeks before admission his legs became weak. He was 'crawling on his knees' and could not walk. Pain in the legs continued. One week before admission he began to walk again, but dragged the left leg. He had had measles three months previously. There was no history of tuberculous contact.

On examination the temperature was normal, he looked well nourished and was in good general condition. In the upper limbs there was no wasting or loss of power and the tendon jerks were normal. The right leg appeared normal on examination. No swelling of either knee was now seen. He limped in the left leg on walking, with some instability of the hip joint, hyper-extension of the left knee, and eversion of the foot. There was generalized hypotonicity and flabbiness of the muscles of the left lower limb, proximally as well as distally, with doubtful minimal wasting of the left thigh and calf. The knee jerks were present and equal on both sides. The left ankle jerk was absent, the right present. There was a yellow follicular exudate in the throat, with slight enlargement of the tonsillar glands. No cardiac murmur was heard; the heart and other systems were normal on examination.

INVESTIGATIONS.—Lumbar puncture produced clear cerebrospinal fluid under normal pressure: cells, fewer than 1 per c.mm.; protein, 91 mg. per 100 ml.; Pandy's test, positive. The Wassermann reaction was negative. The Lange curve was 1123311000. A white blood count gave 6,100 per c.mm. (polymorphs 77%, lymphocytes 17%, monocytes 4%, eosinophils 2%).

The Mantoux test (1 : 10,000) was negative.

The temperature remained normal except for slight intermittent pyrexia up to 99° in the first three weeks. Sulphamezathine, 0·5 g. four-hourly, was given during the first six days. The tonsillitis resolved. Physiotherapy, consisting of assisted active movements, was given daily. By the eighth week of admission the muscles of the left lower limb were almost as strong as on the right side, except for slight residual weakness of the left calf and anterior tibial muscles.

After a stay of nine weeks the patient was transferred to the country branch of the Royal National Orthopaedic Hospital. He was there reported as having no significant paralysis apart from some weakness of the left leg below the knee which was expected to recover fully. There was very slight wasting of the left calf and he walked unaided with the left foot in calcaneus. Physiotherapy was continued and on October 9, 1949, he was discharged home.

Case 3.—A girl aged 23 months was admitted to The Hospital for Sick Children, Great Ormond Street, on September 13, 1950, with a history of weakness in the legs.

Three and a half months before admission she became unwilling to walk when taken out and asked to be carried. She had previously walked normally. During the next three weeks she was irritable. Weakness of the legs and difficulty in walking increased gradually until she could not walk or stand at all. On several occasions she fell down when trying to walk. Her appetite was poor and she seemed thinner since the onset of the illness. There was no vomiting and no history of coryza or cough.

These symptoms followed a vesicular rash, which began two weeks previously, on the right knee, fingers and face. At the same time she seemed fretful and feverish. The rash spread, covering the whole face. Penicillin ointment was applied and the eruption cleared in two weeks. The child's mother had a similar vesicle on her wrist at about the same time.

The patient had been immunized against diphtheria and vaccinated, but no injections of any kind had been given recently. There was a past history of rubella. There had been no recent illness. The parents were healthy and there was no history of tubercular contact.

The child had been previously admitted (on July 27, 1950) to a military hospital in Germany, where it was found that she had marked weakness in both lower limbs with tenderness of the feet and absent knee and ankle jerks. No other abnormality was found on examination.

Lumbar puncture produced clear cerebrospinal fluid with cells less than 2 per c.mm., protein 320 mg. per 100 ml., increased globulin, sugar 70 mg., chlorides 740 mg. per 100 ml., and a sterile culture. Radiography of the spine and skull appeared normal.

Haemoglobin was 98%. A white blood count gave 7,000 per c.mm. (polymorphs 55%, lymphocytes 40%, monocytes 5%).

A diagnosis of infective neuritis was made. Slight occasional pyrexia continued for 10 days and then subsided. Physiotherapy was started and there was some general improvement but progress was slow, although she was moving more freely.

After six weeks in hospital in Germany it was decided to send her to England for further observation to exclude cerebral tumour. The cerebrospinal fluid protein level was still high (300 mg. per 100 ml.).

On transfer on September 13 to The Hospital for Sick Children, Great Ormond Street, the patient appeared an irritable, well-nourished child, unable to walk, but she could now stand on a broad base.

Clinical examination confirmed the findings already obtained in Germany and the diagnosis of acute infective polyneuritis. There was hypotonia of the lower limbs, which were not wasted. Knee and ankle jerks were still absent and there was considerable tenderness of the feet. She appeared to feel pinprick in the lower limbs. Coordination was normal.

INVESTIGATIONS.—On September 14 lumbar puncture showed clear cerebrospinal fluid: cells, fewer than 1 per c.mm.; protein, 180 mg. per 100 ml.; Wassermann reaction, negative. At repeat lumbar puncture on September 21 there were no cells and the protein was 160 mg.

Further radiographs of the skull and spine remained normal and there was no radiological evidence of metallic deposits in the long bones.

The serum Kahn test was negative.

No antibody to herpes simplex was detected in a serum herpes neutralization test.

No pus cells or protein was found in the urine, which in culture was sterile.

On June 26, 1951, the knee jerks were returning and could just be obtained. The ankle jerks remained absent. There was still no wasting in the legs. It was now four and a half months since the child's legs first became weak and as there was gradual improvement with physiotherapy and gain in weight, she was returned to the hospital in Germany to complete her treatment.

Case 4.—A girl aged 2½ years was admitted to The Hospital for Sick Children, Great Ormond Street, on September 1, 1950, with a history of weakness in the legs.

Two months before admission she seemed easily tired and slept badly. Her appetite was poor and she looked thinner. She began to complain of pain in the abdomen and legs. Three weeks later she could only walk from room to room. After a further two weeks she would get out of bed, walk a few steps, then lie down until she was picked up. She 'got weak and went off her legs' and was very miserable.

One month before the onset of these symptoms there was a profuse itching rash, consisting of discrete raised spots on the knees and feet. The rash lasted three weeks and was associated with malaise.

The patient had previously been a lively child who walked well. She had been immunized against diphtheria and vaccinated. There had been no other illness.

On examination her temperature was 98° and pulse 120 per minute. She was pale and miserable with a rather expressionless face and talked in a weak, nasal monotone. She could not sit or stand alone but could walk a few steps if supported.

Examination of the cranial nerves confirmed a mild bilateral facial weakness. This was more evident on the right side and was of a lower motor neuron type. There was marked hypotonia of the neck muscles. Both upper limbs showed generalized flaccidity and hypotonia, more marked in the right limb. There was weakness with minimal wasting. Biceps, triceps and supinator jerks were absent on both sides. The erector spinae and abdominal muscles were weak. Abdominal reflexes were present. The lower limbs were markedly weak, with bilateral foot-drop. The muscles of both calves were tender. There was generalized hypotonia with minimal wasting in the lower limbs. The knee and ankle jerks were absent on both sides. The plantar reflexes were flexor. No cardiac murmur was heard but the heart sounds were poor in quality. Nothing abnormal was found on examination of the lungs or other systems.

INVESTIGATIONS.—Lumbar puncture on September 1 produced clear, colourless cerebrospinal fluid: cells, 1 per c.mm.; protein, 240 mg.; sugar, 63 mg.; chlorides, 705 mg. per 100 ml. A repeat lumbar puncture on September 19 gave cells, 7 per c.mm., and protein, 160 mg.

A radiograph of the spine showed no abnormality apart from spina bifida of the first sacral segment and incomplete fusion of thoracic vertebrae.

Haemoglobin was 98% (13·7 g. per 100 ml.) red blood cells 4,870,000 per c.mm., white blood cells 15,000 per c.mm. (polymorphs 64%, lymphocytes 33%, eosinophils 3%).

A tuberculin jelly test was negative.

A diagnosis of polyneuritis was made and physiotherapy, consisting of assisted active movements, was started. Within two weeks of admission the child had improved generally and the right knee and ankle jerks were faintly present. Eighteen days after admission she seemed happier and her face was more expressive. She was now walking fairly well. The knee and ankle jerks could be obtained on both sides. The child's temperature had remained normal throughout. On September 21 she was discharged home.

When seen as an out-patient one month later she appeared healthy and walked well.

Case 5.—A boy aged 3 years was admitted to The Hospital for Sick Children, Great Ormond Street, on March 8, 1954, with a history of weakness in the legs.

One morning, five weeks before admission, he fell downstairs; no injury was found, but the right leg was subsequently noticed to be weak. Weakness in both legs increased, especially in the 'hip parts', during the next three weeks. The mother noticed when dressing the child that his arms were weak and that he was unable to grip objects firmly. Walking became steadily more difficult until one week before admission he could not rise from the floor, and could only walk a few steps with support. He had slight difficulty in starting micturition. The child's appetite had become very poor.

There had been no previous illness apart from frequent nasal discharge, occasional mild attacks of asthma and bronchitis, and measles, which was not recent. He had never been immunized against diphtheria or vaccinated.

On examination he was a miserable, rather undernourished child, with profuse nasal discharge, who could not walk without help. The cranial nerves were normal. In the upper limbs there was generalized weakness and hypotonia of all muscle groups, with no wasting. The biceps, triceps and supinator jerks were faintly present. Generalized weakness and hypotonia were also present in the lower limbs and they were tender when touched. Both knee jerks were absent, but the ankle jerks were faintly present. Numerous coarse râles were heard in all areas of the lungs. No other abnormality was found.

INVESTIGATIONS.—Lumbar puncture produced clear cerebrospinal fluid: cells, 0; protein, 70 mg.; sugar, 64 mg.; chlorides, 740 mg. per 100 ml.

Haemoglobin was 98% (13·7 g. per 100 ml.) and a white blood count 15,300 per c.mm. (polymorphs 77%, lymphocytes 19%, eosinophils 4%).

A tuberculin jelly test was negative.

No abnormality was found in the urine.

A radiograph of the sinuses showed opaque antra, but no abnormality was seen in the chest.

A diagnosis of acute polyneuritis was made and breathing exercises and gentle assisted active movements were started. One week after admission walking had improved, but there was some hyper-extension of both knee joints. Power was increasing in the arms and the chest was clearer. He was transferred to the Hospital's country branch.

When seen there on April 9, 1954, the patient was still weak on his legs but could walk without assistance. His general condition had improved. Slight hypotonia was still present throughout all limbs. Power had increased but was still below normal in all muscle groups. The tendon reflexes remained unchanged and no wasting had developed.

At the time of writing, muscle power continues to improve gradually.

Discussion

Guillain *et al.* (1916) gave as criteria of their syndrome motor disturbance with loss of tendon reflexes and preservation of cutaneous reflexes, paraesthesiae with slight objective sensory loss, tenderness of muscles, little change in electrical reaction of muscles and increased protein in the cerebrospinal fluid with no cytological reaction. They said that a good prognosis could be given even in the presence of serious paralysis. As the cause they postulated an infective or toxic agent.

The clinical features of later reports have resembled those described by these authors, with the addition of cranial nerve involvement, notably of the seventh nerve. The onset of paralysis often followed a mild pharyngitis or digestive upset. In Debré's cases the invasive period varied from five to 21 days. Paralysis occurred as a flaccid paraplegia, or sometimes involved only the lower limbs. Sphincter disturbances were sometimes described (Ansay, 1937). The importance of watching for dysphagia and taking prompt measures to prevent aspiration pneumonia was stressed by Debré and Thieffry (1951). Sensory symptoms were often mentioned by older children with the disease.

The features of the Guillain-Barré syndrome have also been reported following diseases such as measles, infective mononucleosis and hepatitis. The aetiology of the syndrome remains uncertain.

The albumino-cytological dissociation was found to be non-specific and occurred in other diseases. Dagnelie (1938) pointed out that this feature might be present in the later stages of poliomyelitis. Van Bogaert *et al.* (1938) recorded serial levels of cerebrospinal fluid protein in cases of the syndrome. These showed a maximal level between the twenty-fifth and forty-fifth days of illness. Debré and Thieffry (1951) stated that the maximal level occurred between the tenth and the twentieth day of onset.

The electrical responses of paralysed muscles have been described as diminished, without any reaction of degeneration.

In most patients who recovered the sequelae were minimal. Tendon jerks were often absent months or years after clinical recovery.

Features resembling acrodynia have been described by some authors in cases of the Guillain-Barré syndrome (Van Bogaert *et al.*, 1938; Keizer, 1951). The pathological changes reported have been slight. Degeneration of peripheral nerves has been seen microscopically (Gilpin, Moersch and Kernohan, 1936; Debré and Thieffry, 1951).

Joiner, McArdle and Thompson (1950) studied pyruvate metabolism in an unselected group of patients with polyneuritis. They were able to classify their 40 cases into those in which the blood pyruvate level was normal and those which showed an abnormal rise of blood pyruvate after a test dose of glucose. Of the latter, some responded to treatment with thiamine. Dimercaprol was given to those who did not respond to thiamine. Pyruvate, formed as an intermediate product in the metabolism of glucose, is known to accumulate if there is a failure of the pyruvate oxidase system, when tissue anoxia results. Known causes are thiamine deficiency and the toxic effect of arsenic and heavy metals. Joiner's series included three cases of infective polyneuritis, but these were already in the stage of recovery. The blood pyruvate level was raised in one, but treatment was not given as the patient was already improving. In the other two

cases, the blood pyruvate level was normal. Thiamine and dimercaprol have been administered in cases of the Guillain-Barré syndrome on the assumption that a defect in the pyruvate oxidase system might be present in the neurons (Von Hagen and Baker, 1953). Possibly it would be instructive to study pyruvate metabolism in a series of cases of the syndrome in the acute stage.

In the present series the typical features of acute infective polyneuritis were shown. In all five cases the onset of paralysis was gradual and not associated with high temperatures. Paralysis was proximal as well as distal and did not pick out individual muscle groups. Recovery was good and wasting and permanent changes were minimal. There was a monoplegia in one case, two others had a diplegia and two showed quadriplegia, one of these also having a facial diplegia. Three of the five cases described had a preceding or coexisting

TABLE 1

ACUTE INFECTIVE POLYNEURITIS IN CHILDREN

Authors	Date	Number of Cases	Age and Sex	Mortality	Cause of Death
Monier-Vinard	1925	1	13 M	Nil	
Strauss and Rabiner	1930	1	13 F	Nil	
Sands	1931	2	15 F, 15 M	Nil	
Taylor and McDonald	1932	2	7 F, 7 M	1 (7 M)	Streptococcal sore throat
Meyer	1934	1	6 F	Nil	
Babonneix and Lévy	1934	1	4 F	Nil	
Gilpin, Moersch and Kernohan	1936	5	2½ F, 4 M, 6 F, 12 F, 14 M	Nil	
Sarrouy and Bullinger-Muller	1936	1	6 M	Nil	
Ansay	1937	1	8½ M	Nil	
Laruelle and Massion-Verniory	1937	1	5 M	Nil	
Hecht	1937	7	2 F, 3 M, 3½ F, 7 F, 8 F, 10 F, 10 F	Nil	
Bassoe	1938	1	3½ F	Nil	
Van Bogaert, Philips, Radermecker and Verschraegen	1938	6	4 M, 6 M, 6 F, 12 M, 13 M, 15 M	Nil	
Biemond	1938	2	13 M, 16 M	Nil	
Clément and Kételbant	1938	1	2½ F	Nil	
Giraud and Boudouresques	1938	3	2½ F, 3½ F, 4 F	Nil	
Riser and Planques	1938	3	Not given	Nil	
Gillespie and Field	1939	1	6 M	Nil	
Heernu	1939	1	16 M	Nil	
Susman and Maddox	1940	5	16/12 F, 2 F, 9 F, 12 F, 16 M	1 (16/12 F)	Respiratory paralysis and pneumonia
De Jong	1940	3	9 M, 14 M, 15 M	Nil	
Casamajor and Alpert	1941	3	2½ M, 3 M, 12 F	Nil	
Roseman and Aring	1941	4	4 M, 5 F, 6 M, 7 F	Nil	
Aring and Sabin	1942	1	4½ M	1	Dysphagia, paralysed intercostal muscles and aspiration pneumonia
Kennedy	1944	1	7 M	Nil	
Lewey	1945	1	3½ F	1	Phrenic nerve degeneration
Shaffer	1946	1	8 M	Nil	
Barta and Gerloczy	1948	1	15/12 M	Nil	
Petch	1949	1	13 F	1	Following convulsions
Debré and Thieffry	1951	32	Not given	2	Dysphagia and descending pulmonary infection
Aylett	1954	5	16/12 F, 3 M, 23/12 F, 2½ F, 3½ M	Nil	
Total Cases		99	32 F, 32 M	7	

upper respiratory infection, a feature often mentioned in the literature. A rash preceded paralysis in two cases. In Case 3 this was vesicular in type, and generalized herpes simplex was at one time considered a possible cause but no antibodies were found. Rashes do not seem to have been mentioned before as a feature, except the eruption of varicella, which has been described in association with the Guillain-Barré syndrome (Roseman and Aring, 1941; Clément and Kételbant, 1938). The distribution of the rash was not characteristic of varicella in Case 3 of the present series.

All five patients were under the age of 4 years, the youngest being 16 months. There were three girls and two boys. The cerebrospinal fluid showed the typical finding of a normal cell count and raised protein in all.

There was no mortality in this series. This may have been due to the fact that respiratory infection occurred in only two cases (Cases 1 and 5) and was slight. In 99 collected published cases in children with typical features, seven died (Table). Of 64 cases in which age and sex were given, 27 were 5 years or under (about 42%) and sex incidence was equal. It seems noteworthy that four of the seven deaths were due to pulmonary infection associated with dysphagia or respiratory paralysis. Of these four children, three were under the age of 2 years. It is possible that early detection of dysphagia with the use of parenteral fluids instead of feeding by mouth, with aspiration of pharyngeal secretions, and the use of antibiotics and a mechanical respirator where appropriate might improve the prognosis in such serious cases.

Summary

Five cases of acute infective polyneuritis in children are reported.

The subject is briefly reviewed.

Ninety-nine collected published cases in children are tabulated. This collection shows a mortality of about 7% often associated with pulmonary infection following dysphagia or respiratory paralysis.

I wish to thank Dr. M. Dynski-Klein for permission to publish Cases 1 and 2, Dr. Wyllie for permission to publish Case 3, Dr. P. R. Evans for making available the notes of Cases 4 and 5 for inclusion in this paper, and Dr. W. Sheldon for allowing me to examine Case 5 at Tadworth Court.

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THE TREATMENT OF TICS IN CHILDHOOD

A REVIEW AND A FOLLOW-UP STUDY

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Tics are involuntary movements of the skeletal musculature involving functionally related muscle groups. They are sudden, unexpected, brief contractions, of variable intensity, repeated at irregular intervals, and occur in descending order of frequency from the cephalic to the caudal extremity. They increase in severity during emotional excitement, decrease as a result of distraction or concentration, and disappear during sleep. Tics can be interpreted as biologically purposeful (protective, defensive, or offensive) but serve no apparently useful purpose since their objective is non-existent. In adults they are single and localized, whereas in children they are multiple and migratory. Tics are seen more commonly in boys than in girls and in children than in adults.

In childhood they are found in association with a variety of psychiatric and organic disorders and may occur as a sequel to chorea (Creak and Guttman, 1935) and epidemic encephalitis (Wilson, 1927); in rare cases they are accompanied by echophenomena and coprolalia (Gilles de la Tourette, 1885).

I have not used 'habit spasm', the popular alternative term for tic, because, strictly speaking, a tic is neither a habit (Garrod, Batten and Thursfield, 1934) nor a spasm (Wilson, 1940).

The first systematic treatise on tics was written by Meige and Feindel (1902) and included a comprehensive account of the many methods employed at the turn of the century. A large bibliography has accumulated since then and a very great variety of treatments has been recommended. Sedatives, particularly bromides, as well as 'tonics' have both constantly been advised, though Hobhouse (1939) is one of the few who state categorically that drugs have no place in the treatment of tics; improved hygiene by such measures as fresh air, wholesome diet and change of environment; rest, ranging from bed rest to convalescence; eradication of sources of local irritation or local sepsis, including removal of tonsils and adenoids; various forms of physiotherapy at one time popular and now almost obsolete; advice about school attendance has been contradictory.

The use of suggestion and hypnosis has had few supporters apart from Russell (1910), Fleming (1912), Hassin (1925), Wilson (1927), Brain (1928) and Lust (1930).

Most writers have agreed that some form of psychological guidance is indicated and the procedures recommended have varied from simple advice to prolonged psycho-analysis. The introduction of the psycho-analytical methods of treatment into child psychiatry has influenced both the understanding and the treatment of the tiqueur (Sadger, 1914; Ferenczi, 1926; Deutsch, 1925; Wilder and Silbermann, 1927; Menaker, 1945; Klein, 1948; Mahler, 1949).

Very recent methods such as brief psychotherapy, narco-analysis and group psychotherapy have been employed in selected cases (Lebovici, 1952).

Present Study

This paper forms part of an investigation into the nature, treatment and prevention of tics in childhood which began in May, 1952. It is an attempt to appraise the results of treatment of 96 consecutive tiqueurs referred to the Psychiatric Department of the Royal Liverpool Children's Hospital since May, 1947. These comprise 53 cases investigated in the department before May, 1952, called Group I, and 43 cases investigated by me after that date, called Group II.

The proportion of new cases seen each year up to May, 1953, is indicated in Table 1. The small number of tiqueurs treated in 1947 cannot be accounted for; the large number referred after May, 1952, is directly attributable to the interest shown in this research project. The mean annual referral rate before that date was 5% of the total number of cases, which included every variety of psychiatric disorder in childhood.

It will be appreciated that the treatment of tics in childhood is not solely a psychiatric problem, since all of these patients were sent to hospital by general practitioners, and 62% were referred to the Psychiatric Department by paediatricians.

TABLE 1
ANNUAL REFERRAL RATE OF NEW TIC CASES

Year of Referral	Total Number of Cases	Number of Tic Cases
1947	178	3 (1%)
1948	156	11 (7%)
1949	195	12 (6%)
1950	233	16 (7%)
1951	192	11 (6%)
1952-53	173	29 (17%)

Description of the Sample

The terminology of Barton Hall (1947) has been used throughout this investigation in order to maintain continuity in the recording and assessment of the clinical data.

The following features of the sample studied are considered to be representative of tiqueurs in general, by comparison with cases made available from other sources.

Sex Incidence. There were 63 boys and 33 girls, that is, a ratio of approximately 2 : 1.

Intelligence Rating. The intelligence quotients (I.Q.s) of 89 patients tested by the same psychologist on the Revised Stanford-Binet Scale ranged from 58 to 154 (mean $=106{\cdot}1$, S.D. $\pm 21{\cdot}2$) with an approximately normal distribution.

Age at Onset. This was difficult to ascertain accurately in some cases and was therefore estimated to the nearest half-year. The ages ranged from $3\frac{1}{2}$ to $12\frac{1}{2}$ years with a well-defined peak at 7 years; five tiqueurs were under 5 years at the onset.

Duration of Symptoms. Of the patients 34·4% were examined within six months and 56·3% within a year of onset. The longest interval that elapsed between the onset and referral to a psychiatrist was eight years.

Personality and Body-build. These tiqueurs had many personality traits in common; in descending order of frequency they were restless, sensitive, irritable, stubborn, excitable, phobic, apprehensive and quick-tempered. With few exceptions they were asthenic, wiry children; in no case was the pseudo-Fröhlich habitus, as described by Mahler, Luke and Daltroff (1945), seen.

Sibling Status. The number of siblings per family ranged from one to eight with an average of three. Forty tiqueurs (42%) were eldest children, 22 (23%) were youngest, 11 (11%) were only children, and 23 (24%) were middle children. The equivalent figures of Mahler's series of 33 cases show little correspondence (eldest 30%, youngest 24%, only child 36%, and middle child 9%).

Parents. The majority of parents were anxious, restrictive and rigid; this was not attributable to their advanced age, as suggested by Latimer (1945). The conflicting personalities of parents and tiqueur, and in particular the disturbed mother-child relationship, was found to be a major source of anxiety in the patient.

Family History. The importance of a psychopathic heredity in the aetiology of tics has been stressed repeatedly in the literature, but few and inadequate statistics have been published. Table 2

TABLE 2
FAMILIAL INCIDENCE OF PSYCHOPATHY AND OTHER DISORDERS*

Diagnosis	Parents		Siblings		Grandparents		Aunts and Uncles		Other Blood Relations		Total No.	Total No.
	No. of Individuals	No. of Families	No. of Individuals	No. of Families	No. of Individuals	No. of Families	No. of Individuals	No. of Families	No. of Individuals	No. of Families	No. of Individuals Affected	No. of Families Affected
Tics	20	20	6	5	5	5	5	5	6	3	42	30
Psychoneurosis	34	31	13	11	9	8	7	6	7	5	70	48
Pathological anxiety	53	50	15	15	3	3	14	7	0	0	85	56
Psychopathic personality	2	2	0	0	9	7	0	0	6	4	17	12
Psychosis	0	0	0	0	7	7	2	2	4	3	13	11
Mental deficiency	0	0	6	5	0	0	2	2	1	1	9	8
Rheumatic chorea	5	5	1	1	1	1	2	2	4	4	13	12
Epileptic manifestations	1	1	2	2	3	3	6	6	1	1	13	13

* Information available in 94 cases.

summarizes the familial incidence of psychopathy and neuropathy in this sample and indicates the relatively high proportion of parents with pathological anxiety, psychoneurosis and tics. The adverse influence of such parents on the susceptible child tiqueur will be readily appreciated.

Treatment and Results in Group I

Of the 53 patients investigated before May, 1952, 42 were seen two or three times for clinical investigation, mental testing and parental guidance, and 11 attended the Liverpool Psychiatric Clinic over a period of five to 33 weekly sessions for more prolonged psychotherapy.

In 17 cases the parents were reassured about the child's physical and mental health. A simple explanation of the cause of the tics was given in 35 cases. The majority of parents were instructed to ignore the tics, and 37 were offered advice depending on the nature of the individual problems. Seven children presented school problems, and convalescence was arranged in two cases.

Four patients were referred to the ophthalmologist, three with errors of refraction and one with strabismus. Two cases with nasal symptoms and one with intermittent deafness received appropriate treatment. Two patients were referred to the paediatricians for investigation of abdominal pain and treatment of migraine—ketosis attacks. In three cases the general practitioners were requested to observe the child on account of a rheumatic diathesis. Only one child in the whole series was treated with phenobarbitone.

Results. The results of treatment in this first group were evaluated by means of a follow-up inquiry. Forty-nine of the 53 patients were traced, and of these I re-examined 39, eight were interviewed by a psychiatric social worker, and information about the remaining two was obtained by correspondence.

The information was sufficiently accurate for statistical analysis in only 41 cases, but since they appeared to be fairly representative of the total sample, it is doubtful whether the remaining cases would have influenced the findings to any appreciable degree.

The severity of the tics throughout the investigation was rated on a six-point scale according to a clinical estimate of the frequency, irrespective of the number of concurrent tics:

(5+) Tics repeated continuously every day for a few weeks.
(4+) Tics repeated intermittently every day for a few weeks.
(3+) Tics recurring spasmodically, at intervals of a few days, for a few weeks.
(2+) Tics recurring for a few days at intervals of a few weeks.
(1+) Tics recurring for a few days two or three times a year during periods of marked stress or excitement.
(0) Complete absence of tics for one year.

Progress of Tics. The severity of the tics at follow-up is shown in Table 3. There was a marked improvement as a whole, although only 10 cases (24%) had been completely free of tics for at least a year.

The duration of the tics in the 10 recovered cases ranged from three to eight and a half years (mean = four and a half years); the duration in the other 31 cases followed up ranged from one and a half to eleven years (mean = four and a half years). It is apparent that severe tics persist for several years, contrary to the opinions expressed in many textbooks as to their short duration.

Taking as the criterion of improvement a change of 2+ or more, 31 cases (76%) were improved at follow-up and 10 (24%) unimproved. Of the 34 patients who received brief treatment, 24 were improved, and of the seven patients who received more prolonged psychotherapy, six were improved. Thirteen patients were considered to require further treatment when re-examined; of these only one had had intensive psychotherapy. As a result of the additional psychotherapy, nine patients improved, one was unimproved, and three failed to complete the treatment.

The relationship between progress at follow-up, on the one hand, and sex, intelligence, age at onset, duration before treatment, length of follow-up, age at follow-up, and severity of anxiety, on the other, were considered worthy of further investigation (see Table 3).

SEX. Of the 31 tiqueurs who were improved, there were 20 boys and 11 girls; and of the unimproved there were 10 boys and no girls. The sex difference is significant at the 5% level ($p = 0{\cdot}027$); that is, the prognosis appears to be better in girls than in boys.

There was no statistically significant relationship between improvement and intelligence rating, age of onset or duration before treatment.

LENGTH OF FOLLOW-UP. The average follow-up interval of the improved group was 34·6 months, and that of the unimproved group, 26·7 months. The difference is almost significant at the 5% level ($t = 1{\cdot}743$, D.F. = 39, $0{\cdot}1 > p > 0{\cdot}05$). This suggests that the longer the interval after treatment, the more improvement can be expected.

TABLE 3
RESULTS OF FOLLOW-UP OF CASES IN GROUP I

		Severity of Tics at Follow-up						
		(5+)	(4+)	(3+)	(2+)	(1+)	(0)	Total
Severity of Tics at First Examination ..	(5+) ..	2	4	3	3	3	3	18
	(4+) ..	—	2	1	6	4	5	18
	(3+) ..	—	—	—	1	2	2	5
	Total ..	2	6	4	10	9	10	41
Sex	Male ..	2	6	2	7	7	6	30
	Female ..	—	—	2	3	2	4	11
I.Q.	<70 ..	—	—	—	2	—	—	2
	71–90 ..	—	—	1	1	1	2	5
	91–110 ..	2	3	1	2	3	3	14
	111–130 ..	—	2	—	2	5	2	11
	>131 ..	—	1	2	1	—	1	5
	Not tested ..				2		2	4
Age at Onset (years)	<5 ..	—	1	—	3	—	1	5
	6–7 ..	1	3	2	6	6	3	21
	8–9 ..	1	2	2	1	3	4	13
	10–11 ..	—	—	—	—	—	1	1
	>12 ..	—	—	—	—	—	1	1
Duration before Treatment (years) ..	<1	2	4	3	6	6	7	28
	2–3	—	2	1	1	2	2	8
	4–5	—	—	—	2	1	1	4
	6–7	—	—	—	1	—	—	1
Length of Follow-up (years and months)	1 : 1 – 2 : 0	—	3	2	1	2	1	9
	2 : 1 – 3 : 0	2	2	1	6	3	4	18
	3 : 1 – 4 : 0	—	1	—	2	3	3	9
	4 : 1 – 5 : 0	—	—	1	1	1	2	5
Age at Follow-up (years)	7–9 ..	—	1	—	3	—	3	7
	10–12 ..	2	4	3	4	6	2	21
	13–15 ..	—	1	1	2	2	3	9
	16–18 ..	—	—	—	1	1	2	4
Anxiety Scores*	0–10 ..	—	1	—	4	3	2	10
	11–20 ..	1	2	2	6	2	4	17
	21–30 ..	1	1	1	2	2	1	8
	31–40 ..	—	—	1	—	—	—	1

* In five cases data could not be scored accurately.

AGE AT FOLLOW-UP. The difference between the average ages of the improved and unimproved groups (12 : 2 and 11 : 0 years, respectively) was not statistically significant ($t = 1{\cdot}261$, D.F. = 39, $0{\cdot}3 > p > 0{\cdot}2$). However, all six tiqueurs aged over 15 were improved, as compared with 25 improved of the remaining 35. The difference in proportions improved, although not significant at the 5% level ($p = 0{\cdot}164$), is such as to suggest that tics tend to clear up by puberty. A more prolonged and extensive study is required to verify this conclusion.

INCIDENCE OF ANXIETY. A frequent association between tics and symptoms of anxiety and tension was observed clinically and was confirmed by calculating the frequencies of 17 symptoms included under the following headings: (1) sleep disturbances, (2) tension habits, (3) motor unrest, (4) phobias, worry and poor concentration. The proportion of patients exhibiting the four groups of symptoms was 81, 92, 86 and 83% respectively.

A disconcerting observation at follow-up was that the anxiety symptoms tended to be unaffected by treatment. In order to confirm this, each symptom was graded as to severity on a three-point scale, as described by Miles, Barrabee and Finesinger (1951). The arithmetical sum of the ratings for each patient was termed the 'anxiety score'. Expressing this score as a percentage of the possible total it was found that the severity of the four groups of symptoms was almost identical in the two corresponding samples of treated former and untreated current cases (viz. 22, 27, 41, 35%, and 23, 22, 43, 30% respectively).

It was further shown that improvement in the tics was unrelated to the severity of the anxiety by comparing the anxiety scores of the improved and unimproved groups. The difference between the means (13·4 and 17·3) was not statistically significant ($t = 1{\cdot}250$, D.F. = 34, $0{\cdot}3 > p > 0{\cdot}2$).

Treatment and Results in Group II

Of the 43 patients examined after May, 1952, 19 were seen less than four times for investigation, mental testing and brief psychotherapy, and 24

received more prolonged treatment over five to 29 sessions. The number of interviews was roughly proportional to the severity of the case.

Brief Psychotherapy. A minimum of two interviews was devoted to taking a history, physical and mental examination of the patient, and parental guidance. The informant (usually the mother) was encouraged to ventilate her anxieties, and the confidence of the patient was gained by showing an interest in both his health and in his worries, ambitions, and problems of home and school adjustment.

In every case the parent was reassured concerning the physical and mental state of the child. The tic was interpreted as a safety-valve for tension resulting most commonly from over-correction and restriction. The parent was advised against drawing the patient's attention to the movement and of the futility of punishment. Encouragement of normal activities and interests was advocated. Convalescence was recommended in two cases only in order to remove the patient from a disturbed home, and continued attendance at school was advised except when there was associated physical ill-health.

Physical treatment was required in a small number of cases for threadworms, errors of refraction, dental caries, sinusitis, septic tonsils, enlarged adenoids and otitis media. It was my impression that these sources of irritation aggravated the tics, possibly by lowering the threshold of neuromuscular excitability, and that physical treatment resulted in some degree of improvement. Drugs were not prescribed unless indicated for a complicating physical ailment.

Prolonged Psychotherapy. In the most severe cases treatment was continued at the Liverpool Psychiatric Clinic at weekly intervals. The relationship with the therapist enabled the patients to work through their emotional disturbances by means of drawing, painting, modelling and play techniques, which were selected according to the age, intelligence and symptomatology of the child.

The parents were interviewed at each visit to discuss the patient's progress and management. Emphasis was placed on the harmonious interaction of mother and child as the primary object of treatment. When this was achieved there was invariably an improvement in the patient's clinical condition, and it illustrated convincingly to the mother that the child's recovery depended to a large extent upon her own ability to maintain a happy relationship. It was noteworthy that the patient's progress fluctuated according to the mother's state of health, and in a few cases the mothers were advised to seek treatment for their own emotional disturbances.

Parental Group Psychotherapy. The improvement resulting from correction of parental mishandling was brought out by the following experiment.

Six mothers were invited to form a discussion group and met for one hour each week over a period of 14 weeks during which time the patients received no treatment. Initially common problems were presented for discussion and later individual difficulties concerning the handling of their children were raised and debated. I played an increasingly passive role at these meetings, allowing the parents to advise and criticize each other and intervening only in order to control the discussion. The subsequent modification of parental attitude was acknowledged by every member of the group, and the improvement in the tics was sufficiently pronounced in every case to exclude the possibility of spontaneous remission.

Results. Insufficient time has elapsed to evaluate the final results of treatment but information is available as to the progress of 34 of the 43 current cases observed over a period of one to 20 months. The remaining nine patients comprised the least severe cases in the series and had been given a good prognosis. Of the 34 cases, 28 showed improvement in the severity of the tics. Ten had been treated briefly and of these eight were improved; of the 24 who had received more prolonged treatment, 20 were improved.

Of the 34 patients followed up, the anxiety manifestations were improved in 29 cases. Nine of the 10 patients who had been treated briefly were improved, and of the 24 who had been treated over a longer period, 20 were improved.

Discussion

The apparent confusion in the treatment of tics over the past half-century is the result of the changing concepts of aetiology and of the different aims of therapy. The aetiology remains obscure, but, as a tentative hypothesis, it is suggested that tics in childhood are motor manifestations of psychological and possibly physiological, tension occurring in certain constitutionally predisposed individuals. The underlying source of the tension is attributed to the accompanying psychiatric and organic disorders, and it follows that treatment should deal primarily with the major disorder and only secondarily with the resulting symptoms.

This research has shown that the role of the mother is of paramount importance in the psychogenesis and

treatment of tics. A study of the emotional development of the tiqueur has revealed an over-dependence on the mother throughout the prepubertal period. Maternal anxiety is readily conveyed to the nervous child and disharmony in the mother-child relationship has been identified frequently as a source of emotional conflict in the patient. In the majority of cases modification of parental attitude, increased maternal insight, and attention to the mother's health have brought about improvement in the tics and anxiety symptoms.

It is of interest that a comparison of the outcome of treatment of the former and current cases, that is, two equivalent samples treated along similar lines by different therapists, showed a similar rate of improvement in the frequencies of tics irrespective of the length of treatment. Although the findings are not strictly comparable owing to the large differences between the follow-up periods, they indicate that prolonged psychotherapy is not essential for the successful symptomatic treatment of tics.

It is of some practical importance that the assessments of severity and improvement by the parents were far less stringent than those described here. It was frequently noted that tic-ratings below (4+) tended to be ignored or regarded as unimportant, a change of 1+ was accepted as a marked improvement, and of 2+ as a complete recovery.

An analysis of the symptoms presented by these cases has revealed that tics are correlated most highly with manifestations of anxiety and tension. The tic-frequencies are apparently unrelated to the severity of anxiety symptoms and the latter tend to persist longer than the tics. It has also been found that mild anxiety symptoms improve with brief psychotherapy but severe and multiple anxiety symptoms respond only to prolonged psychotherapy. It is concluded therefore that psychotherapy is the primary treatment of tics in childhood and that the duration should be determined by the severity of the associated anxiety manifestations.

Summary

The literature on the treatment of tics in childhood over the past 50 years is reviewed.

An evaluation of the treatment of a consecutive series of 96 hospital cases by brief and prolonged psychotherapy is described. Fifty-three former patients were followed up after an interval of one to five years; the remainder were investigated and treated by the writer. The results indicate that each form of treatment has been equally effective in reducing the frequency of the tics.

A frequent association between tics and symptoms of anxiety and tension has been observed. Mild anxiety manifestations have improved with brief psychotherapy but severe emotional disturbances have required prolonged psychotherapy.

The significance of the mother-child relationship in the aetiology and treatment of tics is stressed.

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THE RETINOPATHY OF PREMATURITY

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When the condition of retrolental fibroplasia was first described by Terry (1942) in the United States of America it was then only recognized in the advanced state of a cicatricial mass or membrane behind the lens. It is now appreciated, however, that the earliest pathological changes occur in the nerve fibre layer of the retina, which first of all becomes thickened as a result of oedema, transudation and haemorrhage then follow, with subsequent neovascularization and invasion of the vitreous. In cases which do not regress the process ultimately goes on to fibrosis, with detachment of the retina and the formation of a retrolental membrane. In 1950 Heath therefore suggested that the process could best be described as a retinopathy of premature birth.

The first case to be recorded in Edinburgh was in 1948, one more case occurring in that year, four being recorded in 1949, four in 1950, and eight in 1951.

In 1952 we began an examination of premature infants born in the City of Edinburgh.

Clinical

In order to ensure that, as far as was possible, we would be able to follow up the future development of these premature infants we limited our enquiry to premature babies weighing 4 lb. or less at birth whose parents lived in Edinburgh.

We also recalled for examination all babies satisfying the above criteria who had been born in Edinburgh during the years 1948–52. During 1952 each baby was examined as soon after birth as his general condition would permit. On the average, this was possible at about 2 weeks of age, and thereafter the infants were examined at monthly intervals until the age of 6 months.

Ophthalmoscopic Examination. Routine examinations of the fundi were normally carried out without general anaesthesia, the pupils of the infants' eyes being dilated with a solution of 1% paredrine hydrobromide and 1% homatropine hydrobromide. If any ocular abnormality was noted, or if there was any difficulty in obtaining a clear view of the fundi, the baby's eyes were re-examined under general anaesthesia.

General Examination and Investigation. General examination included reference to the following factors:—

IN THE MOTHER. Parity, plural pregnancies, rubella, toxoplasmosis, rhesus factor, diet, antibiotic therapy, length of labour, presentation of the infant, and method of delivery.

IN THE INFANT. Birth weight, degree of immaturity, general management, diet, skin haemangiomata, and antibiotic therapy.

In view of the controversy regarding the possible role played by anoxaemia or by hyper-oxygenation, particular attention was paid to the current practice in hospitals in Edinburgh when giving oxygen to premature babies.

During the period 1948–1952, 1,257 premature infants weighing 5½ lb. or less were born to parents living in Edinburgh; of these babies, 240 weighed 4 lb. or under. Thirteen infants developed diplegia, of whom five also had retrolental fibroplasia. Fifty-one showed other congenital defects such as mongolism, cleft palate, and various limb deformities (Table 1). During this five-year period 20 fully developed cases of retrolental fibroplasia came under our observation. There were, in addition,

TABLE 1

RELATIONSHIP OF MAIN FEATURES OF ALL PREMATURE BABIES BORN AND RESIDENT IN EDINBURGH (1948–52)

Year	Birth Weight 5½ lb. and Under	Birth Weight 4 lb. and Under	True Cases of Retrolental Fibroplasia (all under 4½ lb.)	Babies Showing Cerebral Palsy	Babies Showing Other Congenital Defects
1948	217	52	2	3	15
1949	180	34	4	3	6
1950	280	57	4	2	7
1951	291	51	8*	3	13
1952	289	46	5†	2	10
Total	1,257	240	23	13	51

* One child died while under treatment.
† Three showed spontaneous regression of the eye condition.

three infants (Cases 21, 22, and 23) who, although exhibiting definite signs of the disease, subsequently showed spontaneous regression of the ocular disturbance.

Five further babies are not included. They exhibited doubtful abnormal features on routine ophthalmoscopic examination consisting mainly of small retinal haemorrhages and fullness of the retinal vessels without real tortuosity. All subsequently returned to the normal state and it was hardly considered justifiable to include them as definite cases of retrolental fibroplasia. The degree of visual impairment in the 23 cases reviewed in this survey is analysed in Table 2.

TABLE 2

SUMMARY OF EYE FINDINGS IN 23 CASES OF RETROLENTAL FIBROPLASIA

No. of Cases	Vision		
	None	Partial	Spontaneous Regression to Normal
23	14	6	3

Results of the Investigation

Ophthalmoscopic Findings. Before describing the ocular findings, it is essential to emphasize that, without routine ophthalmoscopic examination, clinical signs do not appear until the eye has been grossly damaged.

It is also important to appreciate that, apart from the pallor of the optic discs which is seen in all babies, the majority of premature infants show a pale greyish-green appearance at the periphery of the fundus not unlike, at first glance, the appearance of a very early detachment of the retina. This appearance was also noted in a number of full-term infants.

The early ophthalmoscopic signs consisted, in most cases, of dilatation and tortuosity of the retinal vessels with an appearance, in certain areas at the periphery, resembling a flat, solid-looking detachment of the retina. These appearances were followed by proliferation of new vessels into the vitreous.

The late signs varied from pale areas, with pigmentary change, mainly at the periphery of the fundi, to retinal folds, or detachment of the retina, and the classical retrolental membrane.

Owens (1951) stated that 60% of cases of retrolental fibroplasia undergo spontaneous regression with no serious residual damage, while Szewczyk (1952) thinks that spontaneous regression may take place at any stage short of advanced retinal detachment. Our own observations are in agreement with the latter statement.

The disease appears always to be bilateral although one eye can be affected to a greater extent than the other. The onset, in so far as clinical signs are concerned, appeared, in our series, usually at 4 weeks although it might be delayed until 12 weeks of age. This is in agreement with the observations of Owens and Owens (1950). The earliest time at which any baby in our survey exhibited definite signs of retrolental fibroplasia was 4 weeks of age. Early ophthalmoscopic examination of these premature infants, with subsequent regular follow-up examinations, revealed, as other authors have emphasized, the frequency of spontaneous regression.

The following records and photographed drawings illustrate some of the changes seen and the ability of the process to undergo spontaneous regression.

Relationship to Birth Weight and Maturity. Most observers have agreed that this form of blindness is confined to premature infants of low birth weight (Chace, Merritt and Bellows, 1950; King, 1950). Griffiths (1951) stated that the incidence rose as the birth rate decreased. In this series three exceeded a birth weight of 4 lb. and only by a few ounces. One infant, although weighing 3 lb. 12 oz. at birth, was claimed to have been born at full term.

In Table 3 is shown the relationship of birth weight to the period of gestation in 187 babies. In a further 33 cases there was no record of the period of gestation, and they are therefore excluded from Table 3. A similar relationship is shown in Table 4 for the 23 definite cases of retrolental fibroplasia that occurred during the period 1948–52.

TABLE 3

RELATION OF BIRTH WEIGHT TO PERIOD OF GESTATION IN 187 CASES

Weights	Under 28 Weeks	28–31 Weeks	32–35 Weeks	36 Weeks and Over	Total
Under 3 lb. ..	1	15	7	1	24
3 and under 3½ lb.	2	15	21	15	53
3½ and under 4 lb.	2	10	56	25	93
4 lb. and over ..	—	1	10	6	17
Total	5	41	94	47	187

Excluded are 23 definite cases of retrolental fibroplasia and 33 cases where there was no record of period of gestation.

From Tables 3 and 4 it will be observed that the susceptibility to retrolental fibroplasia increases as the period of gestation becomes shorter and as the birth weight decreases. This supports the general belief that retrolental fibroplasia is essentially a

disease of prematurity, and is more prone to affect the smallest of these babies.

TABLE 4

RELATION OF BIRTH WEIGHT AND PERIOD OF GESTATION IN 23 CASES OF RETROLENTAL FIBROPLASIA

Weights	Under 28 Weeks	28–31 Weeks	32–35 Weeks	36 Weeks and Over	Total
Under 3 lb. ..	3	3	1	—	7
3 and under 3½ lb.	—	4	1	—	5
3½ and under 4 lb.	—	4	3	1	8
4 lb. and over ..	—	1	2	—	3
Total	3	12	7	1	23

Sex Ratio. Speert, Blodi and Reese (1950) and Ryan (1952) found the sex incidence of cases of retrolental fibroplasia approximately equal. There was no evidence of any sex preference in our present survey. Twelve of the established cases of retrolental fibroplasia in the five-year period were boys and 11 were girls.

Negative Factors. No relationship was found between the development of retrolental fibroplasia and the following factors:—

IN THE MOTHER. Parity, plural pregnancies, rubella, toxoplasmosis, rhesus factor, diet, vitamins and antibiotic therapy, length of labour, presentation of the infant, method of delivery.

IN THE INFANT. General management, diet, vitamins, skin haemangiomata, and antibiotic therapy.

Oxygen. There are four main maternity hospitals in Edinburgh. They will be referred to as Hospitals A, B, C and D.

The results shown in Table 5 are of particular interest. No cases even suggestive of the condition occurred in Hospital C, while it will be noted that approximately 15% of the babies born in each of the remaining three hospitals showed signs in some way suggestive of retrolental fibroplasia. The number of small babies handled by Hospital C was almost the second highest of the four main hospitals. The question therefore naturally arose as to why Hospital C should appear to remain immune from the disease.

Apart from the administration of oxygen, there was no significant basic difference in the management of these infants in the four main hospitals. In Hospital A the infant was nursed in an incubator room, and oxygen was supplied by means of a plastic tent that fitted over the head and shoulders. In Hospital B the infant was nursed in an oxygenaire incubator. In Hospital C the infant was nursed in an incubator room, and oxygen was supplied by means of a plastic tent in which the baby was placed. In Hospital D the infant was nursed in an incubator room and oxygen was supplied by means of a plastic tent which covered the whole body.

Random estimations of the oxygen concentrations attained in the tents showed that in hospitals A, B, and D the percentages were all high (over 60%), while in Hospital C the concentration was even higher (over 70%). All units claimed to have weaned the babies gradually from their oxygen-enriched atmosphere. Unfortunately in many cases the exact duration of oxygen therapy was not recorded.

All but one of the 23 cases of the disease received continuous oxygen therapy. The tendency was for these infants to have been submitted to this environment for long periods. On an average, the infants who developed the disease were kept in oxygen for seven to 10 days longer than those showing no signs of the condition.

In Hospital C, however, in which there were no cases of retrolental fibroplasia, only one infant was recorded as having received oxygen for as long a period as three weeks, the average period of oxygen therapy in this hospital being only five to seven days, although the concentration attained in the 'tents' was higher than in any other hospitals.

Our findings therefore agree with those of Kinsey and Zacharias (1949) and many others, who observed that their cases of retrolental fibroplasia remained, on an average, in oxygen incubators for a

TABLE 5

PLACE OF BIRTH OF ALL PREMATURE BABIES IN THE SURVEY (1948–52)

Degree of Retrolental Fibroplasia	Home	Nursing Home	Hospital A	Hospital B	Hospital C	Hospital D	Total
No signs	21	6	74	39	46	29	215
True cases fully developed	—	—	10	6	—	4	20
True cases of spontaneous regression (1952 only)	1	—	2	—	—	—	3
Doubtful cases of spontaneous regression (1952 only)	—	—	2	2	—	1	5
Total	22	6	88	47	46	34	243

TABLE 6

ANOXIC FACTORS IN 23 CASES OF RETROLENTAL FIBROPLASIA

Case No.	Illness in Pregnancy	True or Apparent Toxaemia	Vaginal Bleeding	Other Anoxic Factors	Total Factors	Anaesthetic Used	Baby in Poor State	Total Factors	Oxygen Given	Infection	Blood Transfusion	Total Factors	Total Anoxic Insults
1	‡		‡		2				‡	‡	‡	3	5
2		‡	‡		2	‡	‡	2	‡	‡		2	6
3		‡			1	‡	‡	2	‡			1	4
4							‡	1	‡	‡		2	3
5	‡	‡			2	‡	‡	2	‡	‡		2	6
6			‡		1	‡		1	‡	‡		2	4
7			‡	‡	2	‡	‡	2	‡	‡		2	6
8			‡		1	‡	‡	2	‡	‡	‡	3	6
9	‡				2				‡	‡		2	4
10	‡				1	‡	‡	2	‡			1	4
11		‡			1	‡		1	‡			1	3
12		‡			1	‡		1	‡	‡		2	4
13							‡	1	‡	‡		2	3
14				‡	1				‡	‡		2	3
15	‡				1		‡	1	‡			1	3
16						‡	‡	2	‡			1	3
17	‡		‡		2	‡	‡	2	‡	‡	‡	3	7
18	‡	‡			2	‡	‡	2	‡	‡		2	6
19						‡	‡	2	‡			1	3
20	‡	‡			2	‡		1	‡			1	4
21	‡		‡		2	‡	‡	2	‡	‡		2	6
22						‡	‡	2					2
23				‡	1	‡	‡	2	‡			1	4
*23	9	7	7	3	27	17	16	33	22	14	3	39	99
†220	55	88	54	—	197	92	69	161	134	92	2	228	586

* Cases of retrolental fibroplasia. † Normal cases. ‡ Indicates anoxic factors.

longer period than the ones showing no sign of the disease.

Anoxia. There are instances of retrolental fibroplasia in babies who have had no oxygen therapy at all (Bembridge, Coxon, Houlton, Jackson and Smallpeice, 1952), and in our survey one of the babies who developed retrolental fibroplasia (Case 22) was never at any time subjected to any form of oxygen therapy. This child showed definite bilateral signs of the condition, which subsequently cleared spontaneously. This seems to indicate that while the administration of oxygen may well be an exacerbating factor it is not the essential basic cause of the disease.

In our series of cases, one other factor stood out quite prominently, namely the presence of anoxia. In Table 6 are listed the 23 true cases of retrolental fibroplasia. It also gives factors acting on the mother which might produce some anoxic insult to the foetus; factors acting at the birth which might produce anoxia in the newborn infant; and factors acting on the child in the neonatal period which might cause an anoxic state. Under the heading of 'other anoxic factors' are included such conditions as gross anaemia and cardiac failure. One mother died after the birth from heart failure, which had been apparent throughout the pregnancy. The use of oxygen was included for one or both of two reasons. The first of these reasons was that it might be toxic to the newborn infant if given in excessive amounts for prolonged periods. On the other hand, an anoxic state might result from removing the baby suddenly from an oxygen-enriched atmosphere to normal room conditions.

Blood transfusion was included by virtue of its administration in cases of anaemia in the child.

From the comparison of the 23 true cases of retrolental fibroplasia with the 220 normal cases (Table 6) it was calculated that the average number of so-called anoxic insults in those infants who developed the disease was 4·3, while in the control group the average number was 2·66.

Ingalls (1948), writing on congenital encephalo-ophthalmic dysplasia, suggested that lack of oxygen was the most important mechanism leading to damage to vascular tissues. Szewczyk (1952) described retrolental fibroplasia as an anoxic retinopathy. He also stated that changes might take place in other tissues, depending on the stage of development of the child at that time, and result in such conditions as cerebral palsy and mental retardation.

If anoxia does play a fundamental role it would seem illogical to assume that the eye alone should always be the site of attack. In this connexion it is of interest to note that no fewer than five of our cases of retrolental fibroplasia also developed cerebral spastic diplegia. This appears to be even more significant when one notes that there were only 11 cases of cerebral palsy among the 240 premature infants with a birth weight of 4 lb. and

FIG. 1.—Female (Case 23) age 4 weeks. Drawing of the right fundus. Dilated and tortuous vessels running towards a greyish white area at the temporal periphery.

FIG. 3.—Female (Case 21) age 3 months. Drawing of the right fundus. Dilated vessels running forward in the vitreous towards a greyish mass of tissue. One vessel bends forward into the vitreous.

FIG. 2.—Female (Case 23) age 4 weeks. Drawing of the left fundus. An appearance resembling a flat, solid-looking detachment of the retina at the superior temporal periphery with dilated and tortuous vessels. There was little change for a further five weeks when regression began. At 12 weeks both fundi were quite normal except for a slight grey appearance at the periphery. At six months both fundi were within normal limits.

FIG. 4.—Female (Case 21) age 6 months. Drawing of the right fundus. The main vessel is now almost normal in calibre. There is a 'ghost vessel' at the site of the former bending. The left eye showed a temporal flattish detachment of the retina which had returned to normal by the fifth month. A final examination at 9 months showed no abnormality except that both fundi appeared pale.

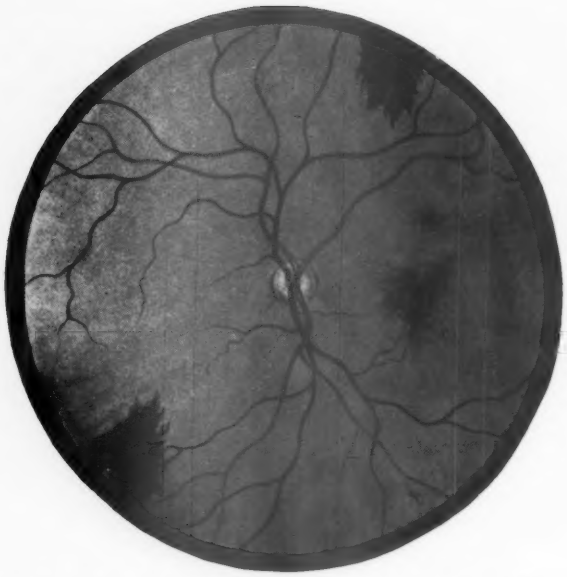

FIG. 5.—Female (Case 22) age 5 weeks. Drawing of the left fundus. A superficial haemorrhage temporal to the disc. Streaky opacities temporally in the anterior vitreous. A greyish white area at the inferior nasal region with some streaky opacities in the anterior vitreous

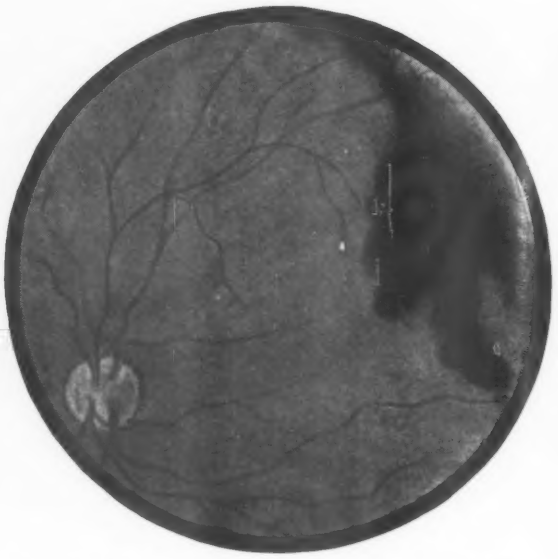

FIG. 7.—Male (Case 5) age 3 months. Drawing of the left fundus. A greyish white mass at the temporal periphery. Running from the region of the ciliary body down into the anterior vitreous is a soft, brownish red mass. At 4 months this fundus had greatly improved and appeared normal at 6 months. Examination at 9 months showed no abnormality except for a greyish discoloration at the extreme temporal periphery with slight pigmentary change.

FIG. 6.—Female (Case 22) age 4 months. Drawing of the left fundus. An area of choroido-retinal atrophy with streaks of pigmentary change at the inferior nasal region.

The right eye also showed haemorrhages and vitreous opacities at 4 weeks which had cleared by 8 weeks. It is noticeable that tortuous and dilated retinal vessels were not seen at any time, though they may have been present before the first examination at 4 weeks.

FIG. 8.—Male (Case 5) age 4 months. Drawing of the right fundus. Vascularized folds occupying most of the lateral half of the vitreous body.

At 6 months there was further progress and at 9 months a complete retrolental membrane was seen in this eye. This case is of particular interest since it demonstrates that spontaneous regression may occur even in a relatively advanced stage of the disease.

TABLE 7
INCIDENCE OF CEREBRAL DIPLEGIA AND RETROLENTAL FIBROPLASIA IN SURVIVING PREMATURE BABIES BORN AND RESIDENT IN THE CITY OF EDINBURGH (1948–1952)

Birth Weight (lb.)	Number of Survivors	Cerebral Diplegia		Retrolental Fibroplasia		Infants with Both Cerebral Diplegia and Retrolental Fibroplasia	
		No. Cases	Incidence per 1,000	No. Cases	Incidence per 1,000	No. Cases	Incidence per 1,000
5½ and over 4	1,017	2	1·96	3	2·95	0	—
4 and under	240	11	45·83	17	70·82	5	20·83
Total	1,257	13	10·34	20*	15·91	5	3·97

* Three cases where the condition underwent spontaneous regression are excluded.

under who were examined in the present review (Table 7). In addition, seven of the 20 fully developed cases of retrolental fibroplasia were considered to be subnormal mentally. The association of retrolental fibroplasia with cerebral diplegia and mental retardation is discussed elsewhere (Ingram and Kerr, 1954), and has been referred to by Scott (1954) in a discussion on this subject.

The main problem seems to lie in assessing the parts played by anoxaemia and by oxygen in the aetiology of the retinopathy.

During our survey the condition was noted in one member of each of six sets of twins. In two of these sets the other partner was recorded as a stillbirth. The remaining four sets of twins continued to thrive, although one partner subsequently died while under treatment with cortisone. Summaries of the case histories of these four sets of twins may be of interest.

CASE 5. Severe maternal toxaemia; anaesthesia used at birth; uniovular twins.

First Twin. Boy, weight 3 lb. 10 oz. In continuous oxygen for two weeks; taken out but suddenly become limp and collapsed. Replaced for one week and gradually returned to normal conditions.

Pronounced bilateral eye changes with spontaneous regression in one eye and complete permanent membrane formation in the other.

Second Twin. Boy, 4 lb. 12 oz. Satisfactory at birth; oxygen for two days; never developed eye abnormalities.

CASE 19. Binovular twins; anaesthesia for second twin only.

First Twin. Girl, 3 lb. 3½ oz. Fairly satisfactory at birth. Oxygen for six days then suddenly discontinued. No abnormal eye signs.

Second Twin. Girl, 3 lb. 3 oz. Limp at birth. Oxygen for at least 12 days. Bilateral retrolental membranes.

CASE 12. Eclampsia; anaesthesia for delivery; binovular twins.

First Twin. Boy, 4 lb. 3 oz. Vertex presentation. Fairly satisfactory but inhaled vomit and had cyanotic attack. Given oxygen for an unknown period; ocular condition treated with cortisone. Died at 4 months. Extensive retrolental fibroplasia.

Second Twin. Boy, 4 lb. 6 oz. Breech delivery. Had cyanotic attacks and given continuous oxygen; probably did not develop any eye abnormality and can now see well.

CASE 3. Eclampsia. Six-hour labour with anaesthesia. Binovular twins.

First Twin. Boy, 3 lb. 12 oz. Assisted breech delivery. Feeble at birth with severe cyanotic attack. Given continuous oxygen for unknown period. Bilateral retrolental membranes at 4 months.

Second Twin. Girl, 4 lb. 3 oz. Vertex presentation. Feeble but cried well. Good colour. Continuous oxygen for unknown period. No evidence of retrolental fibroplasia.

These cases show that one twin only may be involved whether they are uniovular or binovular. As might be expected, in each pair when one partner is involved, the smaller was affected. In addition, in each case, the more anoxic of the two infants, judged by the early post-natal state, was the one more likely to develop the disease.

It appears that anoxia and the prolonged administration of oxygen are the essential factors in the production of retrolental fibroplasia in small premature infants. It may well be that either of these two factors alone is capable of producing retrolental fibroplasia in varying degrees of severity. In this connexion it is of interest to note the recent experimental work of Ashton, Ward and Serpell (1953) upon kittens. They produced vascular proliferation in the vitreous resembling the changes in retrolental fibroplasia. They found that the developing retinal vessels of the kitten became obliterated if the animals were subjected to a continuous high concentration of oxygen. When, however, the kittens were returned to ordinary air the vessels grew again and formed an irregular, extensive growth proliferating into the vitreous. This was often preceded by haemorrhages. The degree of obliteration of the retinal vessels was directly proportional to the degree of im-

maturity of the retinal development, and the concentration of oxygen and the length of exposure to such an environment. A somewhat similar effect was produced if the kittens were subjected to low oxygen concentrations. These experimental findings gave strong support to the impressions created in our survey with regard to the part played by anoxia and the prolonged use of oxygen in the aetiology of retrolental fibroplasia.

The fact that the disease can occur in infants who have never been given oxygen, as in one of our cases, suggests that the administration of oxygen is not the only factor concerned. Ford (1952) has emphasized the importance of asphyxia at birth in the aetiology of spastic diplegia, though he points out the difficulties in evaluating this factor since many babies are deeply asphyxiated at birth without ill effects.

Our conclusion is, therefore, that this form of retinopathy in premature infants is probably part of a general cerebral disorder resulting primarily from anoxaemia. On the other hand, it appears that the administration of oxygen may well, by reproducing retinal vaso-constriction, aggravate the initial disturbance of angioblastic tissue, and may consequently be responsible for the high incidence of the condition in recent years. The duration of oxygen administration seems to be a more important factor than the concentration.

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A CONTROLLED INVESTIGATION OF THE EFFECT OF DIET ON ACUTE NEPHRITIS

BY

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A search of the literature concerning the role of diet in the treatment of acute nephritis revealed numerous expressions of opinion but very little evidence in the form of experimental work on which opinions can be based. The outstanding work is that of Addis (1948), who furnished conclusive evidence that in rats with experimental nephritis a high-protein diet was harmful and caused enlargement of the kidney, while life was prolonged by a low-protein diet. On the basis of this experimental evidence Addis recommended that protein should be considerably restricted in human beings suffering from nephritis, 'for decades if necessary' (Addis, 1940). He recommended that the diet should contain approximately 0·25 g. of protein per lb. per day, together with that quantity of protein which is lost in the urine. Farr and Smadel (1937) had previously shown that when rats with experimental nephritis were given a diet containing only 5% protein the kidney lesion healed rapidly and completely if the acute stage was survived, but if the diet contained 40% of protein the disease progressed and the rats died of chronic nephritis. Experimental nephritis in rats, however, is not necessarily comparable with acute nephritis in human beings, and the quantity of protein given in the high-protein diet (in some experiments up to 70% of the total food intake) was far greater than that which would ever be taken by man.

The only controlled experimental work on human beings which we were able to find was that of Schwensen (1935, 1937), Naeraa (1938) and Mortensen (1947). Schwensen treated six patients (children and adults) with a strict low-protein diet, and compared the duration of albuminuria and microscopic haematuria with that of 34 patients who were given a normal or high-protein diet. He found in the low-protein diet group that albuminuria and haematuria disappeared in an average of 56 days and 73 days compared with 22 and 40 days respectively when a normal or high-protein diet was given. Unfortunately the number of cases in the low-protein group was small, and the method of controlling the study was unsatisfactory. It was not stated how patients were allocated to the different groups. Naeraa (1938) gave 10 patients alternating periods of high- and low-protein diets, and attempted to assess the result by Addis counts. He concluded that there was no increase in the excretion of red cells and casts during the phases of high-protein intake. Mortensen (1947) studied the effect of a high-protein and low-protein diet in 44 patients by the alternate case method. The duration of nephritis was the same in both groups, but albuminuria disappeared more rapidly in the group of patients which was given a high-protein diet.

Below is an account of a controlled investigation into the effect of protein intake on the healing of acute nephritis in human beings.

Method of Study

The diagnosis of acute nephritis was based on a history of symptoms of not more than three weeks' duration, without any history of a previous attack, together with the finding of haematuria, albuminuria, and granular and cellular casts in the urine. Cases of the nephrotic syndrome were excluded, and any case in which there was doubt as to whether the nephritis was acute or merely an exacerbation of a pre-existing nephritis was excluded. Most children showed oedema, hypertension and elevation of the blood urea, but it was not felt that these should be criteria for the diagnosis because they may subside before admission to hospital. All the children were between the ages of 2 and 14 years.

Once the diagnosis was established the treatment was chosen by the random sampling method. The groups were as follows:

Group A: Low-protein Diet. Twenty-two children were included in this group. The quantity of protein given was 0·25 g. per lb. per day, together with

the total daily amount of protein lost in the urine. On this basis the average protein intake was 0·3 g. per lb. per day. The diet was continued after discharge from the hospital until two consecutive normal Addis counts had been obtained. The average duration of protein restriction in the 21 survivors was 293 days (standard deviation 232 days, Table 3). We did our best to ensure that the diet was adhered to, but it is never possible to be sure that departures from a strict diet are not made in the home. Only one surviving child (No. 18) maintained the diet for less than 100 days: he was discharged from hospital to a convalescent home, and it proved impossible to keep him on a low-protein diet.

Group B: Normal Diet. Twenty children were given the ordinary ward diet. Analysis of the ward diet taken by 35 children at intervals throughout the period of study showed that the mean protein intake was 1·23 g. per lb. per day (standard deviation 0·55 g.).

In all other respects the treatment in the two groups was identical. There was no constant policy regarding fluid restriction. The majority of children took what fluid they wanted. Children in both groups were kept in bed until the erythrocyte sedimentation rate was normal and there was no excess of red cells in the ordinary centrifuged specimen of urine.

The investigations in hospital included quantitative estimations of the amount of albumin in the urine, intake and output charts, daily blood pressure readings, a weekly erythrocyte sedimentation rate, and weekly blood urea estimations. An Addis count was performed when the centrifuged deposit of urine showed less than 3 R.B.C.s per high-power field. After discharge the children were seen monthly until the Addis count was normal, and the urine was examined for the specific gravity, the quantity of albumin and the deposit. The blood pressure was recorded, and the blood urea and erythrocyte sedimentation rates were estimated. Patients were re-admitted for Addis counts and renal function tests (water concentration and dilution, and urea clearance) at intervals until the nephritis was regarded as 'healed'. In all, 135 Addis counts were performed, all by one member of the team (M.G.P.). The patients were followed up at less frequent intervals after healing was considered to have taken place. In no case was the period of observation less than one year.

The nephritis was considered to be healed if all the following criteria were satisfied, and remained satisfied at subsequent examinations: (i) The blood pressure was normal. (ii) There were less than 10 mg. of albumin per 100 ml. in the urine. (iii) There were no granular or cellular casts in the centrifuged deposit of urine. (iv) There was less than 1 R.B.C. per high-power field in a centrifuged specimen. (v) The blood urea was less than 40 mg. per 100 ml. (vi) The Addis count showed an excretion of 500,000 R.B.C.s or less per 12 hours. (vii) The renal function tests were normal.

It was very difficult to apply such rigid criteria over a six-year period, and certain departures have been made. These are as follows:—

Isolated specimens of urine from five patients in Group A and seven patients in Group B were found to contain small amounts of albumin during the follow-up period. Table 1 shows the nature of the problem. In all these children the blood pressure and blood urea remained normal throughout the period of observation, the Addis count showed a normal number of red cells and there were no granular or cellular casts in the urine. The specific gravity was normal. Tests to determine whether the albumin was orthostatic were not carried out.

TABLE 1

OCCASIONAL ALBUMINURIA IN PATIENTS WITH 'HEALED' NEPHRITIS

Group	Case No.*	Duration of Observation (years and months)	Total Number of Albumin-free Specimens after Healing	Number of Albumin-containing Specimens†	Number of Normal Specimens after Last Abnormal One
A	1	4·4	8	1 (90)	7
	9	2·9	5	2 (20, 25)	1
	16	3·6	6	1 (75)	2
	17	1·11	3	1 (15)	3
	22	1·11	1	1 (80)	1
B	25	4·2	8	1 (15)	4
	27	3·0	6	1 (30)	4
	29	2·0	7	1 (50)	3
	30	3·3	5	3 (20, 100, 65)	1
	31	3·1	6	2 (25, 70)	2
	33	4·5	6	1 (40)	2
	39	3·8	5	2 (40, 35)	1

* The case numbers were obtained by numbering the completed proformas after arranging the two groups in alphabetical order.
† Quantity of albumin in mg. % in brackets.

It will be seen that in all cases subsequent specimens of urine . albumin-free. In the assessment of the date of healing these isolated abnormal specimens were ignored.

In Case 36 there were seven normal Addis counts, the first of which was two months after admission, and the last one year after admission, but albuminuria persisted for three years after the first normal count. Thereafter the urine was normal, so that the nephritis was regarded as healed 38 months after admission.

In Case 15 there were normal Addis counts two months and six months after admission, but there was a trace of albumin (15 mg. %) in each 12-hour specimen. No more Addis counts were performed, and it was not possible to see the child again until almost a year after admission when the urine was found to be free of albumin. The time of healing was therefore recorded as one year.

In Case 17 the Addis count was normal 11 months after admission, but there was a trace of albumin (15 mg. %) in the 12-hour specimen. Thereafter no further Addis counts were performed, and no urine was examined for a further period of six months. It was then normal, and the nephritis was regarded as healed.

Apart from these exceptions, the criteria for healing were rigidly applied.

Comparability of the Two Groups

In group A there were 10 girls and 12 boys; in group B there were nine girls and 11 boys. The average age in group A was 6 years 1 month (standard deviation 2 years 6 months); in group B it was 6 years 5 months (standard deviation 2 years 2 weeks). The average duration of symptoms before admission in group A was 4·7 days and 4·1 days in group B. Seven children in group A and 11 children in group B had a systolic blood pressure on admission of over 120 mm. Hg; 13 children in group A and 15 children in group B had a blood urea on admission of 40 mg. per 100 ml. or more. The average duration of observation in group A (excluding the child who died) was 30·8 months compared with 31·6 months in group B. It will be seen, therefore, that the two groups are statistically comparable.

Results

There was one death, an 11-year-old boy in the low-protein group. He had a typical acute nephritis, with no suggestion that he had had nephritis before. His condition rapidly deteriorated, and after seven days he was changed to a Borst diet but he died four months after admission. Thus 21 cases remained in this group for analysis.

The results in the remaining children are shown in Tables 2 and 3. It will be seen that there was no significant difference between the two groups. By the time three months had elapsed after admission, 18 in each group had had an albumin-free specimen: 13 in group A and 12 patients in group B had had a specimen of urine which was not only albumin free but had no excess of red cells. Within six months of admission eight in group A and seven in group B had healed; and within a year 16 in group A and 15 in group B had healed. One further child in group A healed and three further children in group B, so that 17 in group A had healed during the period of observation, leaving four who had evidence of persistent nephritis. Eighteen in group B healed, with two showing evidence of persistent activity. As the period of observation in the two groups was comparable (13 in group A and 15 in group B were observed for over two years), this comparison is valid.

The course of the blood pressure and blood urea was not analysed, because of certain omissions in the records. Inspection of the figures, for what it is worth, does not show any difference in the rate of fall of the blood pressure and blood urea in the two groups.

Discussion

Our investigation failed to reveal any advantage in restricting protein in the diet of children suffering from acute nephritis. We can say with certainty that if there is any difference it must be a very slight one, which could only be revealed by studying a much larger number of cases. There was not even a suggestion that children on a low-protein diet fared better than those given a normal diet. Children do not like a low-protein diet, and it should not be used unless it presents definite advantages. The series included several children with a considerable degree of hypertension and with a high blood urea level, but it is possible that if we had had more severe cases it might have been possible to demonstrate some advantage in protein restriction in the acute stage. That, however, is pure conjecture. No child had complete anuria. We would certainly not give such a child a normal diet because of the complex bacterial disturbances which occur in such cases.

The experimental evidence, obtained from a study of animals with experimental nephritis, mostly produced by kidney poisons, may have little bearing on the nephritis of human beings. The aetiology of the nephritis is different, and as we have already

TABLE 2

RESULTS

Case No.	Duration of Observation (Years and Months)	Duration of Diet (Days)	First Albumin-free Specimen of Urine (Days after Admission)	First Albumin-free Urine without Excess of R.B.C. on Microscopy (Days after Admission)	Healed† (Months after Admission)
Group A: Low-Protein Diet					
1	4·4	325	84	119	10
2	3·1	202	15	49	7
3	3·11	232	28	4	3
4	1·0	181	20	21	2·5
5	3·7	1,214	None	None	Not 40
6	1·5	143	28	42	1·5
7	1·9	320	28	154	6
8	2·2	434	90	182	Not 26
9	2·9	146	21	42	1·5
10	3·0	227	56	154	4·5
11	2·4	310	19	19	10
12	1·2	429	None	None	Not 14
13	1·2	241	13	13	Not 14
14	3·1	242	9	9	8
15	3·3	132	14	28	6
16	3·6	353	42	49	7
17	1·11	350	301	336	10
18	1·0	64	48	56	12
19	4·4	162	77	126	16
20	Died	7*	None	None	Died
21	3·2	191	8	22	3
22	1·11	260	6	19	9
Group B: Normal Diet					
23	3·6	—	154	90	24
24	1·2	—	13	210	Not 13
25	4·2	—	56	105	7
26	1·2	—	42	42	4
27	3·0	—	35	56	3·5
28	1·6	—	18	21	5
29	2·0	—	90	90	9
30	3·3	—	23	35	7
31	3·1	—	7	119	8
32	2·1	—	70	105	7
33	4·5	—	154	960	32
34	3·5	—	23	42	2
35	1·2	—	90	119	12
36	3·2	—	45	1,080	38
37	1·0	—	21	21	3
38	2·4	—	29	182	Not 28
39	3·10	—	27	90	10
40	2·6	—	8	42	2·5
41	3·6	—	7	56	1·5
42	2·6	—	90	90	10

* Transferred thereafter to Borst diet.
† In the 'Healed' column, 'Not' with a figure after it, means that healing had not occurred during that period of observation, at the time of writing this paper.

TABLE 3

PROGRESS AND HEALING AT VARIOUS PERIODS AFTER ADMISSION

	Group	Months after Admission								Not Healed during Period of Observation
		0–1	1–2	2–3	3–6	6–9	9–12	12–24	24–48	
Number of cases with first albumin-free specimen	A	12	15	18	18	18	19	19	19*	
	B	10	14	18	20	20	20	20	20	
Number of cases with first albumin-free specimen with no excess of red cells	A	8	13	13	18	18	19	19	19*	
	B	2	8	12	17	18	18	18	20	
Number healed	A	0	2	5	8	12	16	17	17	4
	B	0	2	4	7	12	15	16	18	2

* Persistent albumin during period of observation in two cases.
† Group A consisted of 22 patients on a low-protein diet but one died. Group B consisted of 20 patients on a normal protein diet.

pointed out, the quantity of protein given to animals in the high-protein groups was far in excess of anything which is ever given to human beings. We feel now, in view of the strong evidence that a normal protein intake in acute nephritis in children is harmless, that the onus is on those who advocate severe protein restriction to provide evidence in support of their views.

Summary

Forty-two children aged from 2 to 14 years, suffering from acute nephritis, were allocated by the random sampling method to one of two dietary regimes, severe protein restriction and the normal ward diet. No case was observed for less than a year: the average period of observation was over two and a half years. The two groups were shown to be statistically comparable. Strict criteria for 'healing' were laid down.

There was one death in the low-protein group. In the remaining children no significant difference in the rate of healing was observed.

We concluded that we had been unable to demonstrate any advantage in protein restriction.

Our thanks are due to G. H. Jowett, B.A., Ph.D., and Miss Gibson, of the Department of Mathematics, the University of Sheffield, for statistical assistance, and to all the numerous house physicians and to the ward sisters, especially Sisters Jones, Isaac and Watson, for their cooperation and help in this study. We also wish to thank Miss E. Finch, M.Sc., Mrs. M. J. Walker, Ph.D., and Miss S. Stewart, B.Sc., for the laboratory investigations.

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TRICHOBEZOAR

BY

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Bezoars are rare abnormalities, only about 400 having been described in the literature up to 1950 (Tondreau and Kirklin). Their history presents a strange and intriguing story. From earliest times the bezoars of goats and other animals were used both in the prevention and the treatment of disease. They were worn in amulets as a protection against evil and were taken internally to treat such widely diverse conditions as sexual impotence and leprosy. The word bezoar is derived from the Arabian *badzehr* or the Persian *padzahr*, both of which mean antidote.

At present bezoars are of medical interest in so far as they affect the unfortunate individual who harbours them. The case reported below is the first diagnosed in this hospital in 30 years.

Case Report

M.M., a white girl of 9 years and 10 months, was referred to hospital by the school clinic for investigation of an abdominal tumour.

For some months before admission she had complained of attacks of colicky abdominal pain. She had bouts of nausea with the pain but never vomited. She felt the desire to go to stool but, in fact, never passed a stool in an attack; the pain moved slowly across the abdomen from right to left. Her mother had noticed that during an attack her abdomen became enlarged and she could feel a mass in it. She had always been thin, but her appetite was invariably good.

The patient is the third in a family of four children, and apart from one holiday to the sea has never been away from home. The family have always lived in Johannesburg and have never been to any sheep-farming area. She had a tonsillectomy two years ago and no abdominal mass was felt when she was examined for fitness for the operation.

The child had had no other previous illnesses.

She was an alert, healthy-looking child, with no evidence of anaemia and no abnormalities were detected on inspection. The abdominal contour was not abnormal and no fullness was noticed in the epigastrium. A few scattered lymph nodes were palpated.

On abdominal palpation a large, painless mass was felt in the upper abdomen. This tumour was hard—of almost cartilaginous consistency. It was mobile in a transverse direction but could not be moved vertically. It moved well, at the beginning of respiration. The mass was sausage-shaped and lay at an angle of about 45° to the long axis of the body. Its upper pole disappeared under the ribs just to the left of the midline and the lowermost portion of the tumour reached nearly to the umbilicus. It was possible to get between the upper edge of the tumour and the ribs in the subcostal angle and in this area the liver edge could be palpated, apparently separate from the mass. In the right flank one could get behind the mass. The lower edge of the tumour was irregular. Crepitation was felt over the anterior surface and it was resonant on percussion. The spleen was just palpable. Rectal examination revealed no abnormality. Bowel sounds were heard normally.

Examination of the other systems revealed no abnormality.

Radiographs were taken and Dr. M. J. Meyer reported that the stomach was filled with a mass occupying its

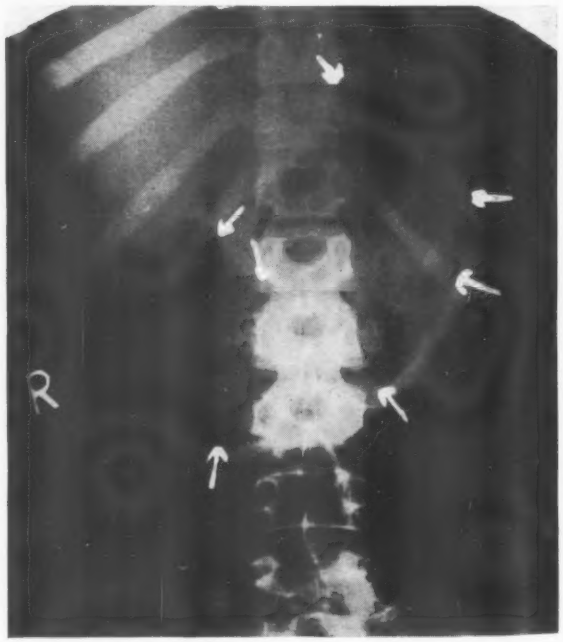

FIG. 1.—Plain film of the abdomen. The stomach is outlined by the mass.

FIG. 2.—Five minutes after the ingestion of barium. The bezoar is outlined by barium. A small amount has already passed on.

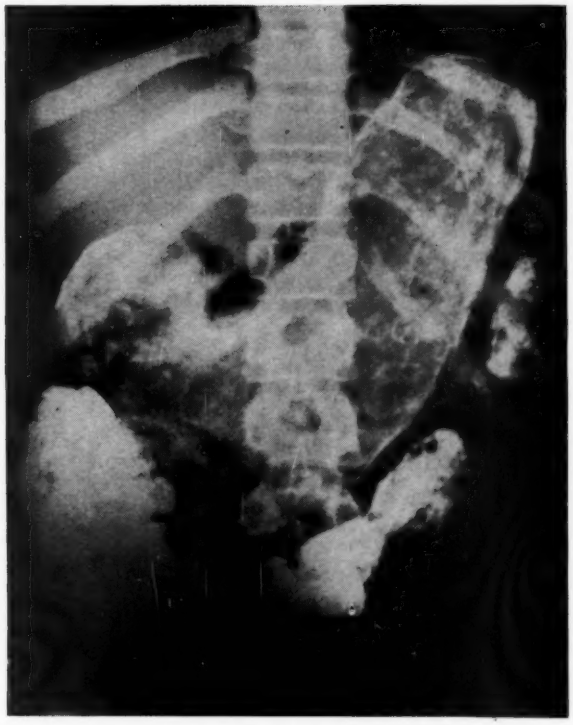

FIG. 3.—Film at six hours. Barium still enmeshed in the trichobezoar. The colon is well filled.

whole volume. A small amount of barium outlined the mass, and passed onwards without delay. The appearances were those of a bezoar, probably due to hair. The lungs were clear.

The parents said that from infancy the child had picked the fluff off her blankets and swallowed it. Of recent years she had been sucking and biting the long strands of her hair and had swallowed them. She was a nail-biter, but had had no other psychological abnormality. She was a year ahead of her age group at school and although she managed to keep up with the school work she came in the lower half of the class. Her elder sisters were both in the top three in their classes. The patient was a happy child and popular with the neighbours and with other children—both her own family and school friends. She was very fond of her younger brother (two years her junior) and had never shown any overt jealousy.

She has now been referred to a psychiatrist for assessment and handling.

The child was operated upon by Mr. R. L. Almond (Senior Surgeon, Transvaal Memorial Hospital for Children). A transverse upper abdominal incision dividing both recti was made. The stomach was found to be three times the normal size and the mass within it felt pultaceous. This was easily delivered through a 3-in. anterior incision in the longitudinal axis of the stomach. The mucosa was found to be greatly hypertrophied with well formed rugae, and lined with a fair

FIG. 4.—Trichobezoar removed at operation.

amount of shiny material. The hair ball itself was very large, the size and shape of the stomach. The dark hairy constituents were held together by shiny material.

The post-operative course was smooth. Gastric suction was maintained for 60 hours during which time the patient was maintained in fluid balance by the administration of intravenous fluids, which were discontinued after about 72 hours. The patient had already been allowed small sips of water which were retained. Thereafter convalescence was rapid and the patient was allowed out of bed after 96 hours and discharged from hospital on the tenth post-operative day.

Stomach fasting-juice on the ninth post-operative day showed normal acidity with a normal amount of free hydrochloric acid.

Discussion

Bezoars are classified into three categories according to their composition: (1) trichobezoars or hair balls, (2) phytobezoars which originate from vegetable matter, and (3) concretions.

Trichobezoars, which are the commonest type, are seen in the younger age groups, the youngest case quoted by De Bakey and Ochsner (1938) being 1 year of age, and are found predominantly in females. These authors found that almost two-thirds of reported trichobezoars were in the second and third decades and a further 17·6% in the first decade. Other cases reported recently by Wilkinson and Wilkinson (1950), Eberhard and Pack (1950), Hurwitz and McAlenney (1951) and Osmond and Price (1951) were all in females in the first two decades. The aetiology of trichobezoars is of two-fold interest: first the purely mechanical aspect of the retention of hair in the stomach and secondly the motivating force behind the ingestion of hair.

No one has adequately explained the mechanics of the formation of hairballs, and experiments done by Meilchen (1911) and Mitchell, Bradshaw and Carlson (1924) seem to prove that the peristaltic movements of the stomach cannot move single hairs but can move intertwined masses of hair; in addition to this, the type of diet, especially its fat content, may bear some relationship to the formation of bezoars. The reason for young girls eating their hair has also not been satisfactorily explained. It is often stated that these cases occur mainly in mentally retarded persons. However, the literature shows that most cases quoted are of a normal mentality although there is frequently some psychological upset or personality change. Bakwin and Bakwin (1953) relate the eating of hair to pica. Golden, in a personal communication to De Bakey and Ochsner, states this is a 'habitual body manipulation' and is related to nail-biting and tongue-sucking and is not a manifestation of abnormal appetite. Both pica and habitual body manipulation are evidences of maladjustment or personality change. The two cases reported by Hurwitz and McAlenney (1951) were both nail-biters, as was one of Eberhart and Pack's (1950) cases and one of the cases of Wilkinson and Wilkinson (1950), and the case reported here. The patient of Nussey and Leask (1949) was reported as being 'rather furtive and reserved to a pathological degree'. Behaviour disorders are no more frequent in girls than in boys and it is difficult to explain the increased frequency of trichobezoars in the female. The explanation of earlier writers is that it is because girl's hair is longer and more easily sucked and bitten.

Trichobezoars are dark in colour, despite the fact that the patient may have fair hair, and consist of firmly intertwined hairs of various lengths. They vary in size with the length of time that trichophagia has been practised. The bezoar may have other types of fibre intermeshed with hair due to the habit that these children have of pulling fibres off blankets, teddy-bears and toys and swallowing them. The trichobezoar usually has a putrid odour due to the breakdown of food material which becomes enmeshed in the tangle of hair. On removal from the stomach they are covered with glairy mucus.

Phytobezoars are composed of vegetable matter, most commonly from persimmons. Thus 73% of the 126 cases of phytobezoar collected by De Bakey and Ochsner were persimmon phytobezoars and Chont (1942) in recording nine cases of persimmon phytobezoar states that probably 90% of phytobezoars derive from them. Tondreau and Kirklin (1950), quoting 16 cases of phytobezoar, state that 13 of them were persimmon bezoars. These cases are confined to Japan and some areas of the U.S.A. and are due to the precipitation by weak solutions of hydrochloric acid of certain constituent matter in persimmons. This becomes a sticky, insoluble mass and binds the seeds and fibres of the fruit into a bezoar. Experiments performed by Chont (1942) and by Izumi, Isida and Iwamoto (1933) tend to prove this hypothesis. Other phytobezoars consist of fibres of vegetable origin bound together in a mass usually too large to pass through the pylorus. Phytobezoars are found mainly in males in the fourth, fifth, and sixth decades and are rare in childhood.

Concretions are usually derived from the ingestion of furniture polish which is highly esteemed for its alcoholic content by certain workers in the furniture industry. Ingestion of water then precipitates the shellac from the polish and this forms a foreign body in the stomach. De Bakey and Ochsner (1939)

record other concretions which have been reported following a barium meal, the ingestion of salol and other medicaments.

Clinical Findings.—The main symptoms are gastro-intestinal, principally pain, which is seen in 90% of cases and is usually of a colicky nature. Anorexia, nausea, vomiting and diarrhoea are seen in a large percentage of cases. Constipation and haematemesis have been reported but are rare. Occasionally the presenting symptom is a mass which has been discovered either by the patient or by her doctor on routine examination. General malaise, loss of weight, headache and weakness are occasionally seen, but the patient's general condition usually remains astonishingly good despite the large mass which is being carried in the stomach.

Persimmon bezoars have a somewhat different history as there is often a story of an acute gastric upset with vomiting and pain following a large feed of persimmons. Following this acute episode the symptoms are similar to those described in the preceding paragraph.

The size varies with the type of bezoar and is usually smaller in the phytobezoar, while the trichobezoar often fills the whole stomach and becomes a cast of that organ. Thus the tumours are usually described as being J-shaped, sausage-shaped, kidney-shaped or cucumber-shaped. While larger bezoars are usually mobile laterally, and move with respiration, smaller ones, especially phytobezoars, are easily movable in all directions within the stomach. Crepitation may be felt over the bezoar in the case of trichobezoars and is an important diagnostic sign when elicited, as in our case. There is frequently a foul, putrid halitosis in the case of trichobezoars.

Laboratory Findings.—There is usually a mild anaemia in these cases and sometimes a mild leucocytosis.

Gastric analysis reveals free HCl in all cases of phytobezoar (Chont) but the gastric acidity may be diminished in trichobezoar. Gastric lavage and examination of the stools may reveal strands of hair.

Radiological Findings.—The diagnosis of bezoar is usually made radiologically.

Trichobezoar and phytobezoar have different radiological appearances. Trichobezoars may show on a plain film of the abdomen as outlining the stomach. The colon may be pushed downwards by the mass. On the administration of barium there is an initial hold-up of the contrast medium which forms a 'cap' to the mass. The barium then flows over the surface of the hair ball and outlines it, at the same time outlining the stomach and proving that there is no abnormality of the gastric outline. As the barium soaks into the matted mass of hair a reticular appearance to the tumour becomes apparent, which persists for some hours after the barium has passed into the small intestine. In our case the barium appeared rapidly in the small bowel, within a space of minutes, due either to a small extension of the bezoar through the pylorus or to a patulous pylorus as a result of several years of abnormal gastric function. The mass remained outlined with barium for several hours. Phytobezoars are usually smaller and do not retain barium as they are solid. They show as filling defects within the stomach and are best seen if a small amount of barium is used. When multiple they show up as multiple filling defects within the stomach, each outlined by barium.

Complications.—Gastric ulceration and intestinal obstruction are the main complications (Tondreau and Kirklin) and occur with equal frequency. Obstruction is more frequently seen in phytobezoars which are smaller and thus more easily able to pass the pylorus. Pieces of trichobezoar may break off and cause obstruction, but this is less common.

Gastric ulcers are seen in some cases and tend to heal after removal of the mass. Very few perforations have been reported, but those that perforate do not do well. In fact the only survival after perforation of an ulcer in the case of trichobezoar is reported by Osmond and Price (1951). Haematemesis has been reported and anaemia is also seen occasionally.

Treatment.—Surgical removal of the bezoar is the treatment which should be carried out in all cases. The operative mortality is given by De Bakey and Ochsner as 4·8% in trichobezoar, 7·4% in persimmon phytobezoars and 4·7% in other phytobezoars. In the nine cases reported by Chont eight were subjected to operation and three died. This is an abnormally high mortality rate as in other series it is much lower.

Prognosis.—On rare occasions recurrence of the bezoar has been reported. If surgical intervention is not succeeded by adequate psychological follow-up, trichophagia may once more be practised. Apart from this possibility, the prognosis is good.

Summary

A case of trichobezoar in a 9-year-old white girl is reported.

A classification of bezoars is given and the clinical

and radiological features and laboratory findings are discussed.

We should like to thank Dr. K. Mills, Medical Superintendent, Johannesburg Group of Hospitals, and Dr. A. E. Strawbaun, Senior Paediatrician, Transvaal Memorial Hospital for Children, for permission to record this case; also Mr. Sewitz, of the Department of Medicine, Witwatersrand University, for taking photographs of the specimen and the radiographs.

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THE VALUE OF RADIOIODINE (I^{131}) IN JUVENILE MYXOEDEMA DUE TO ECTOPIC THYROID TISSUE

BY

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The value of radioactive iodine (I^{131}) in the investigation of disorders of the thyroid gland is now well recognized (Pochin, 1950; Myant, 1952; Wayne, 1954). While I^{131} has been used more frequently in adults than in children, its application to the study of abnormalities of thyroid function has added considerably to our understanding of the varied aetiology and pathogenesis of hypothyroidism in childhood (Hamilton, Soley, Reilly and Eichorn, 1943; Lerman, Jones and Calkins, 1946; Stanbury and Hedge, 1950; Stanbury, 1951; Hubble, 1953; McGirr and Hutchison, 1953; Silverman and Wilkins, 1953; Hutchison and McGirr, 1954).

We present here the results of I^{131} tests in two children which demonstrate the value of these tests in the diagnosis of ectopic thyroid tissue associated with juvenile myxoedema.

The techniques used in the I^{131} investigations have been described elsewhere (McGirr and Hutchison, 1953).

Case Records

Case 1. G.A., a girl, aged 13 years, was first seen by us on October 15, 1953. The second child of three, she was born spontaneously after a normal pregnancy. Her birth weight was 10 lb. She was breast fed and thrived. She sat up at the age of 6 months, walked at 1 year, and spoke single words at 1 year. Her early childhood was uneventful apart from measles, chickenpox, and an operation for squint.

At the age of 11 years she developed tonsillitis and at that time a swelling was noticed under her chin in the mid-line. This was subsequently diagnosed as a thyroglossal cyst and removed in January, 1953. The specimen was reported histologically to be active thyroid tissue. The child's parents had noted that after the operation her speech had become thick and slow, that her hair had started to fall out, and she had become slower in her movements.

On examination the girl was found to be dwarfed (height 127 cm.) and underweight (weight 30·6 kg.). She was typically myxoedematous with coarse features, large tongue, supraclavicular pads, dry scanty hair, and coarse, cold skin. Mentally, however, she was of at least average intelligence. There was a healed scar on the neck at the level of the hyoid bone. The thyroid gland was not palpable. The plasma cholesterol level was 593 mg. per 100 ml. The electrocardiograph showed low voltage with inverted T3. Radiographs of the bones showed no abnormality. The basal metabolic rate was −32%.

RADIOACTIVE IODINE TESTS. On October 26, 1953, she was given by mouth 72 μc. of carrier-free I^{131}. The accumulation of I^{131} in the neck was negligible, amounting to only 7% of the dose at 24 hours, and 3% at 48 hours. Scanning of the neck by means of a Geiger-Müller counter (G.E.C. type G.M. 4) showed that such scanty thyroid tissue as was present was confined to the area of the operation scar (Fig. 1). The urine excretion values

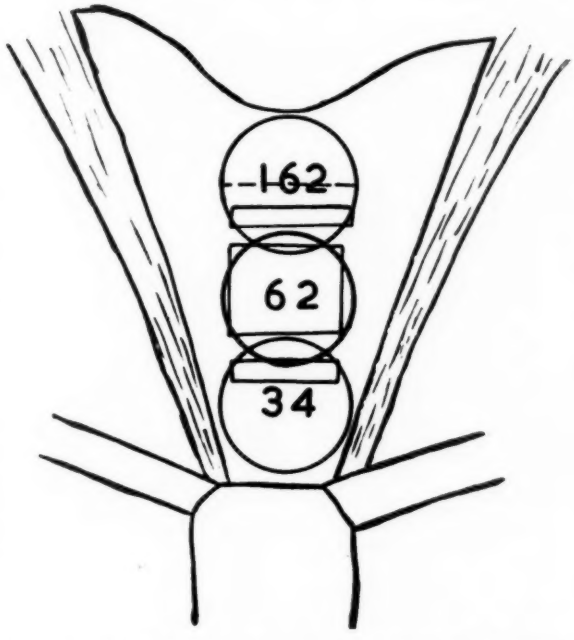


FIG. 1.—G.A. Half-minute counts recorded with G.M. counter placed in contact with skin. Time after dose, 96 hours. Thigh count 10.
Interrupted line indicates site of skin scar.

were 23·3% of the dose of I^{131} for the period zero to six hours; 12·2% for the period six to 24 hours; 20·8% for the period 24 to 48 hours. The total plasma radioactivity 48 hours after the dose of I^{131} was 0·89% of the dose per litre of plasma. The protein-bound fraction was 0·12% of the dose per litre; the butanol-extractable I^{131} was 0·10% of the dose per litre.

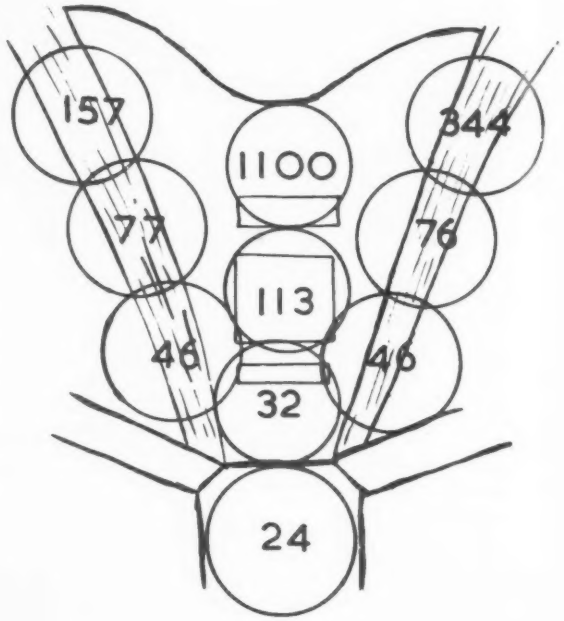
TREATMENT AND PROGRESS. On dry thyroid, gr. 1 daily, the girl has completely lost her myxoedematous features. Mentally and physically she is more active and in the first five months after starting treatment she has grown 5 cm. in height.

Case 2. S.M.J., a girl, aged 7½ years, was referred to us on November 30, 1953, because of failure to grow. An only child, she was born spontaneously after a normal pregnancy. Her birth weight was 7 lb. 14 oz. She was breast fed and thrived. She walked and spoke single words about the age of 15 months but did not cut her first tooth until the age of 16 months. She had always been constipated. Within a year of going to school at the age of 5 years she had measles, mumps and chickenpox. She had done well at school and was in the normal class for her age.

Her parents had become increasingly concerned by her failure to grow since she was 3 years of age, and recently her class-mates had begun to tease her about her small stature.

FIG. 2.—Photograph of S.M.J. illustrating dwarfism and somewhat infantile proportions in contrast with control of same age.

FIG. 3.—S.M.J. Half-minute counts recorded with G.M. counter placed in contact with skin. Time after dose, 24 hours. Thigh count 9.



On examination it was apparent that the child was dwarfed (height 104 cm.) and underweight (weight 17·68 kg.). Mentally she was above average intelligence. She had rather a dry, cold skin, a small umbilical hernia, showed a tendency to supraclavicular pad formation, but otherwise did not present the characteristic appearances of myxoedema (Fig. 2). The thyroid gland was not palpable in the normal position or elsewhere. The tongue looked normal even when examined with a laryngeal mirror. The blood cholesterol level was 183 mg. per 100 ml. The electrocardiograph showed low voltage in the three standard leads. Radiographs of the bones showed the ossification of a child at the age of 3 years.

RADIOACTIVE IODINE TESTS. On December 15, 1953, she was given by mouth 40 μc. of carrier-free I^{131}. The accumulation of I^{131} in the neck was 30% of the dose at 24 hours. Scanning of the neck by means of a Geiger-Müller counter showed that there was no thyroid tissue in the normal site, and that the only thyroid tissue was in the region of the base of the tongue, just above the hyoid bone (Fig. 3). The urine excretion values were 20·0% of the dose of I^{131} for the period zero to six hours; 22·5% for the period six to 24 hours; 6·4% for the period 24 to 48 hours. The total plasma radioactivity 48 hours after the dose of I^{131} was 0·84% of the dose per litre of plasma. The protein-bound iodine fraction was 0·36% of the dose per litre, and the butanol-extractable I^{131} 0·28% of the dose per litre.

TREATMENT AND PROGRESS. There has been a striking improvement in the child's health, mental and physical, on dry thyroid gr. 2 daily. Her constipation has been completely corrected and in the first four months after starting treatment she has grown 5·2 cm. in height.

Discussion

Radioactive iodine has been used previously to confirm the diagnosis of ectopic thyroid tissue (Feitelberg, Kaunitz, Wasserman and Yohalem, 1948; Nachman, Crawford and Bigger, 1949; Crispell and Parson, 1950; Schilling, Karr and Hursh, 1950; Sicher, 1953). In all of the cases cited by these authors, however, the ectopic tissue, which was lingual, was producing local symptoms, such as swelling at the back of the tongue and difficulty in swallowing, and the diagnosis had already been made on clinical grounds alone. As far as we know our second case is the first patient in whom the diagnosis of ectopic thyroid has been determined by I^{131} tests alone and in the absence of local signs and symptoms.

Neither of these two children had thyroid tissue in the normal site. They were dependent for their thyroid hormone on the activity of the thyroid tissue at the base of the tongue. For a time both children had developed normally and it may be assumed that the thyroid hormone produced had been adequate for their needs. Ultimately, however, the body's demands outgrew the productive capacity of the available thyroid tissue, and signs of hypothyroidism appeared. The existence of a hypothyroid state in Case 1 even before operation is suggested by the degree of dwarfing found only nine months later. In this patient the ectopic thyroid tissue had visibly enlarged, and was removed under the erroneous belief that it was a thyroglossal cyst. It is probable that this visible enlargement had occurred because of excessive stimulation by thyrotrophin produced in response to a state of hypothyroidism. Nevertheless, the enlargement had failed to compensate for the fundamental lack of tissue and to supply enough thyroid hormone. Removal by operation of virtually all the thyroid tissue available to the patient had resulted in the development of the typical clinical features of myxoedema. In the absence of local symptoms the ectopic thyroid tissue might have been better left alone, and it should be possible in future to avoid such mistakes in diagnosis by the application of radioactive iodine tests to all mid-line swellings of the neck. In S.M.J., who was undoubtedly hypothyroid but without the gross features of myxoedema, the ectopic thyroid tissue had not become palpably enlarged by the time she was first seen.

In hypothyroidism protein-bound I^{131} in the plasma is usually negligible. It came, therefore, as a surprise to find that 48 hours after the ingestion of I^{131} by these patients there should be measurable amounts of protein-bound I^{131} in their plasma, namely, 0·12% and 0·36% of the dose per litre in G.A. and S.M.J. respectively. The finding that 0·10% and 0·28% of the dose per litre respectively were extractable by butyl alcohol, and not re-extractable by 5% Na_2CO_3 in 4N NaOH, suggests that the protein-bound I^{131} was mainly in the form of thyroxine or a thyroxine-like substance.

Blom and Terpstra (1953) have reported values for protein-bound I^{131} of 0·43% and 0·19% per litre at 48 hours in two patients who had become hypothyroid following subtotal thyroidectomy for thyrotoxicosis, and whose serum protein-bound I^{127} was low, namely, 1·3 μg. % in each patient. An attractive explanation of the appreciable amounts of protein-bound I^{131} found in such hypothyroid patients has been put forward by Riggs (1952), Blom and Terpstra (1953) and Wayne (1954) to the effect that scanty but very active residual foci of thyroid tissue, under intense stimulation with thyrotrophin, and with no storage capacity for organically bound iodine, are working to the maximum of a diminished capacity to meet the body's needs for thyroid hormone, and are turning over the iodine presented to them so rapidly that a relatively large proportion of the thyroid hormone molecules produced and released into the circulation contains radioactive atoms. Unfortunately, in our patients we were not able to estimate the levels of protein-bound I^{127} or to establish by chromatography that the thyroid hormone and not a premature thyroxine-like compound was being formed, and so we were unable to confirm the correctness of the hypothesis outlined above in relation to them, although obviously it would fit the facts of both cases.

Conclusions

Consideration of all the features of these two patients lends support to the opinion that some cases of childhood hypothyroidism may result from an insufficiency of thyroid hormone, which is relative and progressive rather than absolute (Hubble, 1953). Such a quantitative deficiency may arise, as in our patients who had no thyroid tissue in the normal site, from the ultimate failure of ectopic thyroid tissue to synthesize sufficient thyroid hormone for the body's needs.

Our experience in children suggests that the protein-bound I^{131} which may occur in hypothyroidism may arise in different ways. The

hypothesis discussed above, which envisages the rapid production of inadequate amounts of hormone with an unusually large number of its molecules labelled with I^{131}, affords a probable explanation of the appreciable amounts of I^{131} found in hypothyroid patients with scanty thyroid tissue. The high levels of protein-bound I^{131}, which we have previously reported in non-endemic goitrous cretins, appear to require a different explanation and to be due to an intrinsic defect in the synthesis of the thyroid hormone (Hutchison and McGirr, 1954).

Summary

The clinical features of hypothyroidism in two children, who were investigated with I^{131}, are presented.

The I^{131} studies indicated the absence of thyroid tissue in the normal site, and revealed that the only thyroid tissue was situated above the hyoid bone at the base of the tongue.

The value of scanning the neck for I^{131} accumulation in patients with mid-line neck swellings and in unexplained cases of juvenile myxoedema is discussed.

A probable explanation of the presence of appreciable amounts of protein-bound I^{131} in hypothyroid patients with scanty thyroid tissue is considered.

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NEONATAL ASCITES ASSOCIATED WITH URETHRAL OBSTRUCTION

BY

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The end of the nineteenth century saw the beginning of a gradual change in the study of the pathology of the foetus and the newborn infant, largely as a result of the work of Ballantyne in Edinburgh. The interest in the examination of grossly deformed monsters was already giving way to the study of foetal conditions which were compatible with life. At this time Fordyce (1894) reviewed 63 cases of foetal ascites, including one case of his own, and showed that, although ascites was frequently associated with gross congenital anomalies, it also occurred with relatively minor evidence of disease in other organs. It remained for Dorland (1919) to distinguish true ascites from other conditions giving rise to marked abdominal enlargement at birth, amongst which he included distension of the urinary bladder, generalized anasarca, congenital polycystic kidneys, cystic degeneration of the liver and fluid distension of the genital tract.

We have been able to find records of 103 cases of foetal ascites in the literature, a number of which showed gross abnormalities of the urogenital or alimentary systems, while others showed only hypertrophy and dilatation of the urinary tract with or without a demonstrable urethral obstruction. A variety of conditions was found in the remaining cases, the most common being chronic peritonitis, usually of obscure origin (Hoffman, Sternberg and Rascoff, 1951); syphilitic hepatitis, cirrhosis of the liver, obstruction of the portal vein and cardiac failure were rare causes of ascites.

The present cases both had urethral obstruction in the absence of other gross anatomical abnormalities.

Case Reports

Case 1. K.C., a boy, aged 6½ weeks, was the fourth child of a 37-year-old mother. Pregnancy and labour were normal, and the mother's Kahn reaction was negative. His birth weight was 5 lb. 12 oz. (2,600 g.). He was an obvious mongol; slight abdominal distension which was noted at birth persisted during the neonatal period. He gained weight slowly and for 48 hours before admission to hospital at the age of 4½ weeks he had about eight watery stools daily and vomited occasionally.

On examination there was marked abdominal distension, especially of the upper abdomen where there were dilated abdominal veins; there was a small umbilical hernia and bilateral inguinal herniae. Shifting dullness was demonstrated in the abdomen but no masses were palpable. The urine was normal and contained 2 g. chlorides per litre. The baby was noticed to be passing normal amounts of urine although these were not measured.

He was treated with oral fluids for gastro-enteritis but the stools remained frequent although there was no further vomiting. A diagnostic abdominal tap produced clear, straw-coloured fluid containing 40 cells per c.mm., mostly lymphocytes; it contained 130 mg. of protein per 100 ml. The following day 20 oz. (568 ml.) of similar fluid were removed by paracentesis; subsequent palpation revealed no enlargement of liver or spleen and no masses were felt. The ascites rapidly accumulated and 10 days later a further 30 oz. (852 ml.) of fluid were removed. The fluid had a specific gravity of 1010 and contained 126 cells per c.mm. (88% lymphocytes); the protein content was 500 mg. per 100 ml. and urea 40 mg. per 100 ml. The blood urea was 44 mg. per 100 ml. The baby's condition steadily deteriorated and he died four days after the last abdominal tap with a provisional clinical diagnosis of portal hypertension.

NECROPSY FINDINGS. The body was that of a somewhat emaciated male infant weighing 2,690 g. (5 lb. 15 oz.) and measuring 47 cm. in length. The face, hands and feet showed mongolian features. The abdomen was markedly distended with a circumference of 37·5 cm. (cf. circumference of thorax, 29 cm.). There were bilateral reducible inguinal herniae and a small umbilical hernia. Both testes were palpable in the inguinal canals.

The peritoneal cavity contained about 500 ml. of clear, pale yellow fluid. The viscera were normally arranged and the peritoneum was not inflamed.

Both kidneys (Fig. 1) were moderately hydronephrotic, the renal tissue having a thickness of 3 to 6 mm. and showing fairly clear differentiation into cortex and medulla. Near the upper pole of the right kidney was a small cyst, 3 mm. in diameter, which contained a little clear fluid.

The ureters were dilated, tortuous and hypertrophied. Each had a diameter of 6 to 8 mm.

The bladder contained a little pale urine. Anteriorly

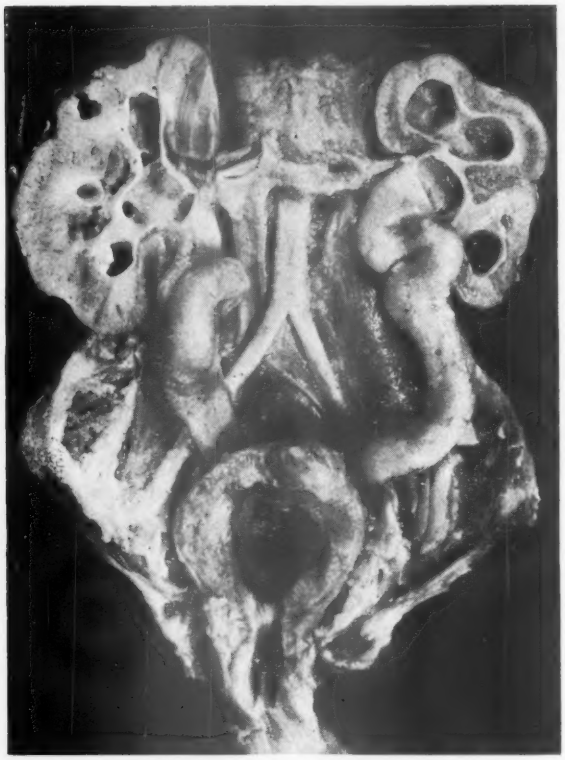

FIG. 1.—Urinary tract of Case 1 showing urethral valve, vesical hypertrophy, and dilatation of ureters and pelves.

and laterally its wall was 5 to 6 mm. thick, mainly the result of muscular hypertrophy although the mucous membrane was slightly thickened and haemorrhagic. In the midline posteriorly the bladder wall was of paper thinness over an area measuring 1·6 × 1·3 cm. which contained no demonstrable muscle and appeared to be formed mainly from peritoneum. At the apex of the bladder was a small urachal cyst measuring 1·0 × 0·6 cm.

The posterior urethra was dilated and hypertrophied. The verumontanum was prominent and attached to its lower end were two folds of mucous membrane forming a typical urethral valve.

Apart from patchy collapse of both lungs posteriorly, all other organs were normal.

MICROSCOPICAL EXAMINATION. The left kidney showed distortion of the cortex by scattered small cystic spaces lined by flattened epithelium. These were separated by renal tissue in which tubules were relatively scanty, glomeruli were of normal infantile type and packed closely together, and there was a considerable increase of interstitial tissue. The right kidney was normal.

Section through the greater part of the bladder showed marked muscular hypertrophy with a normal mucosa covered by transitional epithelium. Posteriorly, however, the muscle rapidly thinned and then stopped abruptly leaving areas where the wall was composed of a little loose connective tissue covered by a single layer of flattened epithelium (Fig. 2).

Both lungs showed extensive collapse with a number of small pneumonic foci.

All other organs were normal.

Case 2. D.R., a boy, aged 11 weeks, was delivered at home by vertex presentation in the thirty-fourth week of pregnancy. Delivering the abdomen was difficult. The birth weight was estimated at between 4 and 5 lb. As no urine was passed during the first 24 hours of life, he was admitted to hospital. There was marked abdominal distension and the abdomen was tympanitic above the umbilicus and dull to percussion below it. There was a hydrocoele of the left scrotum. The blood urea concentration was 50 mg. per 100 ml.

A radiograph showed a large, dense opacity in the lower abdomen displacing the intestine upwards. Under general anaesthesia the prepuce was slit dorsally and a fine bicoudé catheter passed per urethram. During the next 24 hours 2½ oz. (71 ml.) of urine drained through the catheter. The abdominal distension remained, dullness to percussion appeared in both flanks, and the abdominal wall became oedematous, so 5 ml. 'diodone' was injected through the catheter, and a radiograph showed it concentrated in a small bladder and less concentrated behind the bladder. These findings suggested rupture of the bladder (Dr. C. J. Hodson). Laparotomy (performed by Mr. V. A. J. Swain) at the age of 48 hours showed

FIG. 2.—Photomicrograph of bladder wall (Case 1) showing localized absence of muscular coat (× 11).

much clear, yellow fluid in the peritoneal cavity; the bladder was small and thick walled and there was a hole in its fundus where it was adherent to a loop of small intestine. Both ureters were dilated and the kidneys appeared normal. The hole in the bladder was repaired and a suprapubic cystostomy performed.

Intravenous fluids were given for 36 hours after operation and recovery was satisfactory. The urine drained well through the cystostomy tube and contained a trace of protein and a little blood.

At the age of 10 days the abdomen became distended again, severe vomiting began, and drainage through the suprapubic catheter ceased. As ascites was again evident, tubes were inserted through each flank into the peritoneal cavity under general anaesthesia and much clear yellow fluid escaped on both sides and continued to flow satisfactorily for 24 hours. Abdominal paracentesis on the twelfth and thirteenth days of life produced about 40 ml. of fluid on each occasion.

At 13 days urine began to drain through the suprapubic tube and thereafter the infant's condition steadily improved and he gained weight despite a period of paralytic ileus at the age of 20 days and the development of anaemia requiring blood transfusion. The blood urea level, which had risen to 102 mg. on the sixth day of life, fell to 29 mg. per 100 ml. at 27 days. The urine was kept alkaline with potassium citrate and was not infected; it always contained varying amounts of protein with a few pus cells. The measured urinary output was about 9 oz. (256 ml.) daily. The serum electrolyte levels were essentially normal throughout.

At 5 weeks of age the baby had a short episode of diarrhoea during which a specific *Esch. coli* was isolated from the stools, but the infection rapidly responded to aureomycin.

Despite his well-being the blood urea level was rising and had reached 112 mg. by the age of 7 weeks. At 8 weeks the suprapubic tube blocked; drainage was re-established but the catheter slipped out a week later and when re-introduced did not drain any urine. Diodone injected into the catheter showed that the dye passed into the small intestine. The blood urea level had increased to 221 mg. per 100 ml. Ten days later the baby passed no urine for five days and two days after the flow of urine had begun again spontaneously he died suddenly.

NECROPSY FINDINGS. The body was that of a male infant weighing 3,080 g. (6 lb. 13 oz.) and measuring 50 cm. in length. The abdomen was distended and tympanitic with a protuberant umbilicus and a circumference of 36 cm. (cf. circumference of thorax, 32 cm.). An old right paramedian operation scar continued at its lower end into a cystotomy wound from which a little pus exuded. Both testes were in the scrotum.

The peritoneal cavity was largely obliterated by fine fibrous adhesions binding the loops of small intestine together but it also contained about 20 ml. of pale clear fluid.

Both kidneys showed considerable reduction in the thickness of the renal tissue with poor differentiation between cortex and medulla. There were occasional small irregular cavities up to 1·5 mm. in diameter in the medulla. The pelves were moderately dilated but had a smooth lining. The left kidney was about twice as large as the right kidney.

The ureters were dilated to 6-7 mm. in diameter, tortuous and hypertrophied.

The bladder was contracted and had a muscular wall about 1 cm. thick with mild hyperplasia of the mucosa. In the fundus a small hole measuring 2 × 1 mm. had been partially closed by a catgut suture but allowed communication between the bladder and a smooth-walled, cystic space, 1 cm. in diameter. The latter was firmly adherent to a loop of ileum and was surrounded by fibrous adhesions. No leakage into the general peritoneal cavity or the small intestine from either the bladder or the cyst could be demonstrated.

The posterior urethra was dilated and hypertrophied. The verumontanum was prominent and continued inferiorly into two prominent folds of mucosa running downwards and around the urethra forming a typical congenital urethral valve.

All other organs appeared normal.

MICROSCOPICAL EXAMINATION. Both kidneys showed much interstitial fibrosis with infiltration with lymphocytes, plasma cells, and occasional eosinophilic polymorphs. The glomeruli were reduced in number and many were fibrosed or hyalinized. Small cysts lined with flattened epithelium were in the medulla. There was no evidence of pyelonephritis.

The 'cyst' communicating with the bladder was lined with lymphocytes, plasma cells, and phagocytes, and showed a little smooth muscle in its otherwise fibrous wall.

All other organs were normal.

Discussion

Twenty-two cases of undoubted ascites associated with dilatation of the urinary tract have been described in the literature; the majority were stillborn or died soon after birth. In one case (Hicks, 1864) both ureters were occluded in their lower thirds although the bladder contained a little urine and the urethra was apparently not examined; Bruce (1870) found an anatomically patent urethra although the right ureter did not communicate with the bladder; Moreau's case (1828) showed dilatation of the bladder but he did not describe the urethra, whereas Edgecombe (1930) found no urinary obstruction apart from phimosis.

An organic urethral obstruction was demonstrated in the remaining 18 cases. In four infants both urethra and anus were imperforate (Duncan, 1870; Gilles, Roques and Lefèvre, 1914; Hunter, 1932; Gercken and Knepper, 1937), the rectum or sigmoid colon ending blindly behind a grossly dilated bladder or communicating with it through a persistent cloaca.

In 14 children there was urethral obstruction with varying degrees of urinary tract dilatation but no abnormalities of the alimentary or other systems.

Since the majority of the earlier cases were recorded because of the obstetrical problems arising from the foetal abdominal distension, a detailed anatomical description of the urinary tract was frequently lacking and the sites and types of urethral obstruction poorly described. Some had atresia of the urethra (King, 1837; Williams and Galabin, 1878); others a membranous septum (Ballantyne, 1893). Porak (1895) described a typical urethral valve, while others mentioned only the presence of a stricture usually in the posterior urethra (Eden, 1904; Luker, 1913). The bladder was invariably distended and often hypertrophied and megalo-ureters usually coexisted. Hydronephrosis was often absent (Eden, 1904; Luker, 1913), while hypoplasia of one kidney (Williams and Galabin, 1878) or polycystic renal disease (Porak, 1895) was sometimes seen. Magyar (1946) described the presence of a patent urachus.

The most recently reported cases have shown congenital urethral valves. Parrott (1951) described a 28-day-old boy who died with grossly infected kidneys, and one of Lord's cases (1953) survived for five weeks. James and Davis (1952) described a boy who was operated on when 3 weeks old; a urethral obstruction was broken down and the child was well at 8 months of age.

The relationship between ascites and urethral obstruction has been discussed by Lord (1953) who stated that leakage or transudation of urine from the bladder, ureters, or kidneys appears to be the most plausible cause of hydroperitoneum. Reliable data pointing to such a pathogenesis, however, are not generally available. Actual perforation of the bladder was described by King (1937) in a foetus of four months' gestation who had complete atresia of the posterior urethra with marked dilatation and hypertrophy of the bladder, bilateral megalo-ureters, and small kidneys. A hole 1·3 cm. long was situated just behind the summit of the bladder and allowed a free flow of urine into the peritoneal cavity, the fluid in which contained fibrin. Case 2 showed a similar perforation of the bladder; although it could be argued that this was caused by preliminary catheterization, the adhesions around the rupture suggest that the lesion was of longer standing.

Duncan (1870) described a stillborn infant with atresia of the urethra 5 cm. below the neck of the bladder with a communication between the large intestine and bladder. While the muscular coat of the lower two-thirds of the bladder was about 1 cm. thick, in its upper third the vesical wall consisted of peritoneum and mucous membrane only. This was a lesion similar although more extensive to that found in Case 1, and strongly suggests the possibility that urine may have passed directly across this thin membrane and accumulated in the peritoneal cavity.

In no case has obvious leakage from the kidneys been demonstrated, although thin-walled renal cysts are frequent (Lord, 1953), and Porak (1895) described one very voluminous cyst in the left kidney of his case. Baar (1954) has recently seen a child who lived only two minutes in whom the peritoneal cavity contained about 400 ml. of fluid; the bladder was hypertrophied and the urinary tract dilated without any organic urethral obstruction. A thin-walled cyst about 6 cm. in diameter was situated just beneath the capsule on the anterior surface of the right kidney. It is possible that fluid may transude from such a cyst into the peritoneal cavity without actual rupture.

Summary

Two male infants with congenital urethral valves and ascites occurring in the neonatal period are reported. In one case muscle in the wall of the bladder was partially lacking, in the other the bladder ruptured.

It is suggested that in the presence of urethral obstruction, ascites is due to the accumulation of urine in the peritoneal cavity following leakage or transudation from the urinary tract.

We wish to thank Dr. J. N. O'Reilly and Dr. R. H. Dobbs for permission to publish the clinical details of these cases, Dr. C. J. Hodson for his reports on the radiological findings, and Mrs. F. M. Byron for her technical assistance.

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CHRONIC MYELOGENOUS LEUKAEMIA IN INFANCY

BY

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Chronic myelogenous leukaemia is an uncommon disease in infancy and is usually termed congenital in cases seen at or within a few days after birth. The latter do not appear to differ from those seen later except that they are believed to have started during intra-uterine life, and Kelsey and Andersen (1939) have laid down certain criteria for the diagnosis, which might be briefly stated as symptoms present at, or within a few days after birth accompanied by a disease process which could be reasonably concluded to have started during intra-uterine life. The condition is not transmitted from mother to foetus; Forkner (1938) collected 21 cases of chronic myelogenous leukaemia associated with pregnancy where the infant was healthy.

The clinical picture is one of hyperleukocytosis with immature forms of the myeloid series. There is a constant thrombocytopenia in all cases. The spleen is markedly enlarged, as is also the liver but to a lesser extent. Varying degrees of haemorrhagic manifestations are always seen and are frequently the initial sign. This tendency to bleed is more in keeping with the picture of acute leukaemia. Death is usually due to haemorrhage. The lymph nodes are not constantly enlarged but enlarged cervical nodes have been recorded. The average duration of the disease appears to be about one year irrespective of treatment.

Poncher, Weir and Limarzi (1942) recorded a case of congenital leukaemia in an infant aged 6 weeks. The early symptom was progressive enlargement of the abdomen and petechiae of the eyelids and mouth. This patient was treated with blood transfusions and x-ray irradiation using the spray technique. The infant died at 3 months. Cross (1944) reported two cases under 1 year from a series of six cases of chronic myelogenous leukaemia and in addition mentioned 16 cases collected from the literature between 1921 and 1942. The ages of these latter cases ranged from newborn to 3 months. Keith (1945) described the case of a 3-month-old infant whose initial symptom was rectal bleeding and was found to have an enlarged spleen and liver with slight enlargement of the cervical lymph nodes. This patient survived for 12 months and was treated with small blood transfusions. Cooke (1953) reported three cases under 1 year from a series of 15 cases of chronic myelogenous leukaemia in childhood. Two of these babies were aged 3 months and one was aged 8 months. These three cases were treated with blood transfusions and the average survival time was one year. The treatment was also discussed in this paper, and Cooke concluded that benzol, arsenic, urethane, radio-active phosphorus and irradiation with x-rays are best confined to periods during which definite symptoms, such as splenic enlargement or pressure symptoms, require relief. The best results were obtained from x-ray therapy. Anaemia and haemorrhagic symptoms were somewhat relieved by blood transfusions.

A further case of this disease in an infant under 1 year is described here. The mode of onset appeared to be unusual.

Case Report

A girl aged 9 months had recurrent swelling of the fingers and dorsal surfaces of both hands during the previous three months. Her mother thought that the condition was connected with the administration of sulphonamide for a respiratory tract infection. The baby had been quite well otherwise. The mother had had a course of thiouracil for a toxic goitre before her pregnancy with a moderate result and no ill effects.

On clinical examination the baby was seen to be a well nourished infant who appeared somewhat irritable. The fingers and dorsal surfaces of both hands were slightly puffy and rather blue. There was no tenderness and the finger joints were freely mobile. The swelling was confined to the phalanges and metacarpal bones. There was a small area of bruising around both nipples. The spleen was hard and enlarged about two fingerbreadths. The liver was just palpable. The lymph nodes in the neck and axillae were slightly enlarged. No other abnormal findings were detected. The temperature was normal but subsequently there were elevations to 100° F. for periods of two to three days. The urine was normal. The Mantoux test (1 in 1,000 O.T.) was negative but a crop of petechiae appeared around the site of the

injection. Radiographs of the chest, long bones and hands were negative. A blood examination gave Hb 70% (Sahli), red blood cells 3,900,000 per c.mm., white blood cells 80,400 per c.mm. (undifferentiated blast cells 0·5%, myeloblasts 0%, promyelocytes 0·5%, myelocytes 5·5%, metamyelocytes 5%, polymorphonuclear cells 46·5%, lymphocytes 28·5%, monocytes 8·5%), platelets 3,000 per c.mm., Group O, Rh-positive. An iliac crest puncture was carried out and was followed by marked bleeding into the surrounding tissues. The marrow film showed myeloblasts 1·2%, promyelocytes 5·8%, myelocytes 43·4%, metamyelocytes 7·6%, polymorphonuclears 32·4%, basophilic normoblasts 0·2%, polychromatic normoblasts 4·2%, orthochromatic normoblasts 5·2%.

During the baby's stay in hospital there was little change in her general condition. The spleen and nodes became larger. A fine purpuric rash appeared during the second week, mainly over the face and chest. She was given a blood transfusion and discharged home after two and a half months in hospital. The differential white cell count on discharge showed little change since admission. The fingers and hands had returned to normal and a further radiograph was negative. She attended the out-patient clinic during the following five months, remaining quite bright and active. The haemorrhagic signs became much more marked and she had extensive areas of ecchymosis with a widespread purpuric rash. The white blood cells numbered over 100,000 per c.mm. on several occasions, the number of primitive cells increased and the platelets were scanty or absent. A further blood transfusion was given with little benefit and no improvement in the haemorrhagic tendency.

She was readmitted at the end of five months as her condition had deteriorated. A differential white cell count at the time showed an increase in the primitive cells. Radiographs of the long bones were again negative. As the disease had become acute it was decided, with little hope of success, to try the effect of A.C.T.H. An initial dose of 20 mg. followed by 10 mg. daily was given for 14 days. No change in her general condition was noted and there was no alteration in the blood picture. She was allowed home following a third blood transfusion.

She was observed from time to time during the following three months. The spleen became much larger and lymph nodes could be felt in the abdomen. Though the child remained fairly active it was obvious that the increase in size of the spleen was causing discomfort. It was decided to readmit her to hospital with a view to x-ray therapy. On this occasion a differential white cell count showed undifferentiated blast cells 2%, myeloblasts 6·5%, promyelocytes 12·5%, myelocytes 10·5%, metamyelocytes 5%, polymorphonuclears 50%, lymphocytes 11·5%, monocytes 2%. Platelets numbered 15,000 per c.mm. Three days after admission she collapsed and died within a few minutes.

Necropsy Report

The essential findings were as follows:

The lungs showed numerous small haemorrhages and a few firm consolidated foci suggestive of leukaemic infiltration. The hilar glands were slightly enlarged and fleshy.

The spleen was greatly enlarged, pink and soft, with innumerable small pale follicles scattered throughout.

The mesenteric nodes were enlarged. Their cut surface was pink with paler areas and occasional haemorrhages.

The liver was enlarged and pink with pale trabeculations in parts.

The vessels of the circle of Willis were normal. There was an extensive haemorrhage in the right lobe of the cerebellum, and it had ruptured into the subarachnoid space. A smaller haemorrhage was in the left cerebral hemisphere above the lateral ventricle.

The pulp of the spleen was extensively infiltrated by cells of the myeloid series but the Malpighian bodies were still distinct. All members of the myeloid series were present, myeloblasts and myelocytes predominating; eosinophils were plentiful but basophils were very scanty. Numerous mitotic figures were seen. There were few, if any, primitive red cells. The appearances were typical of chronic myeloid leukaemia. Leukaemic infiltration similar in type was found in lungs, liver, kidneys and lymph nodes.

Summary

A case of chronic myelogenous leukaemia in an infant aged 9 months is described.

The case was treated with small blood transfusions and A.C.T.H. It was doubtful if the treatment influenced the course of the disease.

The literature is briefly reviewed.

We wish to thank Dr. J. L. Markson for his assistance in the interpretation of the blood films and Dr. H. Thompson for the necropsy and histological reports.

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NON-ENDEMIC GOITROUS CRETINISM

BY

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Enlargement of the thyroid gland is an unusual finding in cretins outside endemic goitrous areas. Wilkins, Clayton and Berthrong (1954), reviewing published cases of non-endemic goitrous cretinism, collected reports of 32 cases and described a further four cases of their own. Other cases have been reported by Rienhoff (1940) and Smallpeice (1949).

The hypothyroidism in these cases is of variable degree and the thyroid enlargement may appear at any time from infancy to adult life. Early administration of thyroid extract in adequate dosage causes the enlarged thyroid to return to normal size unless irreversible pathological changes have taken place in the gland. Subsequent withdrawal of the drug or reduction in dosage results in reappearance of the goitre. In glands which have been removed the histological changes are broadly those of hyperplasia leading to involution and fibrosis. Radioactive iodine studies have so far been reported in 26 cases (Hamilton, Soley, Reilly and Eichorn, 1943; Lerman, Jones and Calkins, 1946; Stanbury and Hedge, 1950; Stanbury, 1951; Hubble, 1953a; McGirr and Hutchison, 1953; Wilkins *et al.*, 1954) and have shown that the enlarged thyroid glands have an unusual avidity for iodine, unlike cases of non-goitrous sporadic cretinism in which there is little or no uptake of radioactive iodine.

From these facts the aetiology of non-endemic goitrous cretinism would appear to be a complete or partial failure of production of thyroid hormone with, presumably, an excessive secretion of pituitary thyrotropic hormone resulting in hyperplasia of the thyroid gland. An identical condition may also be produced by the action of goitrogenic agents and is known to occur in the newborn infant following administration of thiouracil to the mother during pregnancy (Elphinstone, 1953). The high incidence of the disease in siblings suggests that the defect is genetically determined, possibly by a recessive mode of inheritance.

The rarity of this type of cretinism and the value of radioactive iodine studies in elucidating the exact nature of the defect of thyroid synthesis have stimulated this report of a further case.

Case Report

Elizabeth C., an only child, was born at term weighing 7 lb. 13 oz. The mother's pregnancy had been normal but breast feeding was not established and the infant was fed on National dried milk. No abnormality was noticed by her parents until the onset of vomiting, stridor and difficulty in taking feeds at the age of 6 weeks. When first examined at 8 weeks the infant's appearance was suggestive of cretinism and there was enlargement of the thyroid gland; the blood cholesterol was 130 mg.%. The vomiting ceased and no treatment was prescribed.

When admitted to The London Hospital at the age of 4 months the features of cretinism were definite but not gross (Fig. 1) and there was a diffuse enlargement of both

FIG. 1.—Elizabeth C., aged 4 months, showing the cretinous facies.

lateral lobes of the thyroid gland, which was palpable but not visible. The tongue protruded from the mouth and there was some inspiratory stridor considered to be due to the large tongue. A small umbilical hernia was present. The infant was miserable, pale and inactive, and took only small feeds very slowly.

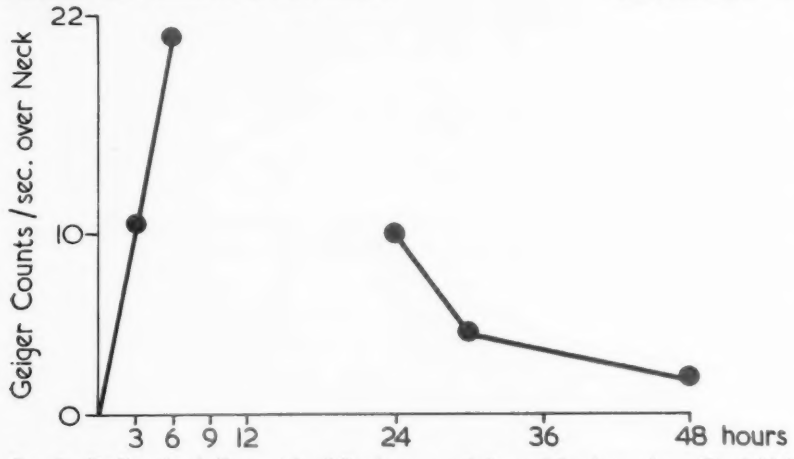

FIG. 2.—Radioactive iodine uptake following an oral dose of 2 microcuries. The initial uptake is high and rapid. Most of the I^{131} has been released by 48 hours.

Initial investigations showed anaemia (Hb 9·6 g.%) and a raised blood cholesterol level (307 mg.%). The electrocardiogram was normal and the radiological bone age was not retarded. The results of radioactive iodine studies are discussed below.

As soon as the investigations were completed treatment was begun with dried thyroid, ¼ grain daily, the dose being increased gradually to ¾ grain daily. After six weeks of thyroid therapy there was complete remission of the cretinous features, the infant was happy and normally active, and the thyroid gland was no longer palpable.

The family history is of considerable interest. The parents are not related by blood and there is no history of thyroid disease in any other member of their families. The mother has been deaf since an attack of measles at the age of 7 years. She first noticed a swelling in the neck at the age of 15, and a partial thyroidectomy was carried out when she was 22 years old. Histological section of the thyroid showed simple colloid goitre. The father is a deaf-mute and he, too, had a goitre, first noticed at the age of 8, and removed by partial thyroidectomy at the age of 23. The pathological appearances of his thyroid gland were those of nodular colloid goitre. Neither parent has ever had symptoms of hypo- or hyperthyroidism. There is no history of residence in an endemic goitrous area or exposure to any goitrogenic agent.

Radioactive Iodine Studies

Method. Carrier-free radioactive I^{131} was given by mouth. The thyroid uptake was assessed by placing a lead-screened Geiger-Müller counter over the enlarged thyroid and recording the number of counts per second. Several readings were taken and the mean calculated.

Results. Following a dose of 2 microcuries there was a rapid uptake of I^{131} by the thyroid gland, a high level being reached within six hours (Fig. 2). The peak level was not determined but at 24 hours the level had fallen considerably and by 48 hours most of the accumulated I^{131} had been released. These findings indicate that the patient's thyroid gland can take up iodine and does so with an avidity suggestive of a thyrotoxic gland. The rapid release of I^{131} suggests a failure of conversion of iodide to an organic form in which it could be stored in the gland.

Further information was obtained by an experiment with potassium thiocyanate (KSCN) which blocks the uptake of I^{131} and causes the immediate release from the thyroid gland of any iodine, normally only a very small quantity, not converted to an organic, protein-bound form (Vanderlaan and Vanderlaan, 1947). In order to magnify the effect the dose of I^{131} was doubled in this test and the high uptake was again demonstrated (Fig. 3). Four hours after administration of I^{131} and two hours before the expected high level in the thyroid, 250 mg. KSCN was given by mouth. There was an immediate

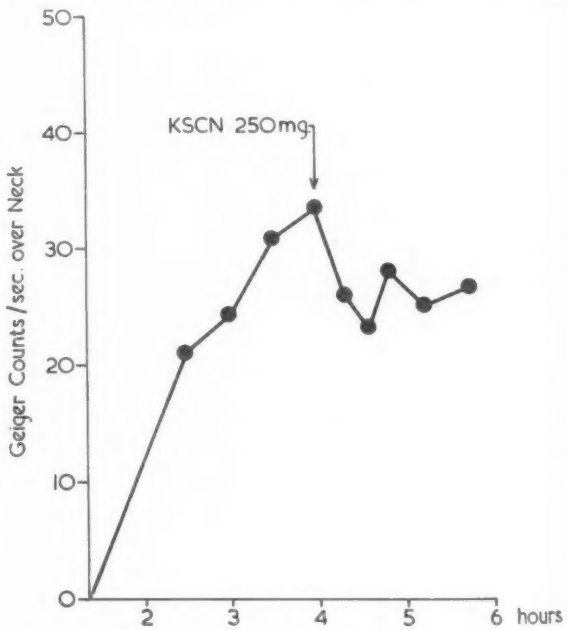

FIG. 3.—Radioactive iodine uptake following an oral dose of 4 microcuries. Administration of KSCN after four hours results in an immediate loss of approximately 30% of the accumulated dose.

fall in the count over the neck of approximately 30%. This result indicates that at least one-third of the radioactive iodine accumulated in the thyroid gland after four hours remained in an inorganic, unbound form.

The mother's radioactive iodine uptake was also investigated and was found to be normal.

Discussion

Results of radioactive iodine studies in previously reported cases have shown that the defect in non-endemic goitrous cretinism may occur at different stages in the elaboration or secretion of thyroid hormone. In almost all cases the ability of the thyroid gland to take up iodine to an unusual degree has been demonstrated, and it is in the subsequent behaviour of the gland that the differences arise. Hamilton *et al.* (1943) found thyroxine in the thyroids of two patients after removal and suggested that there was a failure to release the hormone from the gland. In one of the cases reported by Hubble (1953a) thyroxine was present both in the removed gland and, in small quantities, in the plasma. In this case it was considered that the failure of production was quantitative rather than qualitative. In a group of 12 cases McGirr and Hutchison (1953) obtained results which showed the defect to be in the final synthesis of the thyroid hormone from an organic iodine precursor. In only four previous cases has the response to KSCN shown the defect to be a failure of conversion of inorganic iodide to organic iodine compounds (Stanbury and Hedge, 1950; Stanbury, 1951). In these patients, whose ages ranged from 13 to 23 years, there was an immediate release of 70 to 90% of the accumulated dose of I^{131} after administration of 1 or 2 g. KSCN.

The results obtained with radioactive iodine suggest that the case reported here is probably of the latter type, the first to be reported in this country. The fact that only about 30% of the iodine uptake was expelled by KSCN may be explained either by the presumption of a partial rather than a complete failure of conversion or perhaps by the fact that the arbitrary dose of 250 mg. KSCN chosen for an infant of 4 months was too small to obtain a maximum effect. Further confirmation of the abnormality of the infant's thyroid would have been obtained from a study of the protein-bound iodine level in the plasma and by observing the effect of a larger dose of KSCN. This was not undertaken in the first instance in view of the risk to the patient of continuing to withhold thyroid therapy, but at a later date, when the infant's growth and development are established, it is intended to complete the investigations in full.

A perplexing aspect of this case is the significance of the colloid goitres in both the parents. The possibility of endemic goitre was considered in the father's case in view of the recognized association between this condition and deaf-mutism (Hubble, 1953b). However, in the absence of any family history of endemic goitre or of residence in an endemic area this diagnosis could not be upheld. Since neither parent has ever shown symptoms of hypothyroidism, and the mother has a normal radioactive iodine uptake, it is possible that the goitres in the parents are purely coincidental. It would, however, be more satisfactory, especially in view of the strong genetic factor in goitrous cretinism, to explain the occurrence of goitres in three members of a family on the basis of a similar defect. Such an explanation is, in fact, possible if it is assumed that the parents had suffered a minimal deficiency of thyroxine production which, in the periods of increased demand for hormone during childhood, had led to recurrent hyperplasia of the thyroid followed by involution, in a successful attempt to overcome the tendency to hypothyroidism. This train of events would explain the development of a colloid goitre. The subsequent maintenance of a euthyroid state, particularly after partial thyroidectomy, is difficult to explain although the demand for thyroid hormone might now be so small as to be met by even a diminished amount of imperfectly functioning thyroid tissue.

From a genetic point of view, in order to explain the incidence of what is probably a recessive defect in both parents of an affected individual, it is necessary to postulate an incompletely recessive gene which is responsible in the heterozygous parents for a mild form and in the homozygous infant for a severe form of the disease. This is undoubtedly labouring the theory and it must be concluded that the significance of the goitres in these parents is not at present completely understood.

Summary

A case of non-endemic goitrous cretinism is described.

The results of radioactive iodine studies indicate a failure of conversion of inorganic iodide to organic iodine compounds.

The significance of goitres in both parents is discussed and it is suggested that the abnormal gene in this family is an incomplete recessive.

The author wishes to acknowledge the advice and encouragement given by Dr. Richard Dobbs by whose permission the case is published. The radioactive iodine studies were devised and carried out by Dr. A. S. Mason of the Medical Unit, The London Hospital, whose experience and technical advice have been of great

assistance. Suggestions concerning the genetics of the case were made by Dr. H. Harris.

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THE TREATMENT OF HYPOPLASTIC ANAEMIA AFTER CHLORAMPHENICOL

BY

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The first reports of the use of chloramphenicol in human subjects appeared in 1948 (Ley, Smadel and Crocker; Payne, Knaudt and Palacios) and in these patients toxic effects were not observed. In 1950 Volini, Greenspan, Ehrlich, Gonner, Felsenfeld and Schwartz gave chloramphenicol to two patients suffering from typhoid fever and one patient suffering from brucellosis, and they observed a marked fall in the peripheral white cell count, especially affecting the polymorphonuclear leucocytes; the lymphocyte and monocyte counts remained unaffected, and after stopping the drug the white cell count returned to normal. Gill (1950) reported similar changes in the white cell count of two infants aged 4 months and 13 months, and in these patients the haemoglobin level and red cell count remained unaffected. Rich, Ritterhoff and Hoffmann (1950) described the first fatal case of aplastic anaemia in an adult following chloramphenicol therapy, and similar fatal cases in children were reported by Hawkins and Lederer (1952) and Wolman (1952) in this country and by Sturgeon (1952) in America.

Osgood (1953) has reviewed the mortality rates for aplastic anaemia in the United States of America and has claimed that they have not increased since chloramphenicol became available. In spite of this, some writers (Franklin and Garrod, 1953) feel that a potentially toxic drug such as chloramphenicol should not be used, while others recommend its use only in exceptional circumstances. Hodgkinson (1954) has investigated the incidence of blood dyscrasias associated with chloramphenicol in the British Isles, but he did not give details of the treatment received by these patients except to state that three of them were still being maintained by blood transfusion. It might be helpful to clinicians encountering similar cases to record our experience with the treatment of a patient suffering from hypoplastic anaemia after chloramphenicol.

Case Report

A boy aged 6 years was admitted to hospital for investigation of anaemia. He had been well until 17 weeks before admission when he developed acute bronchitis and was treated with chloromycetin palmitate, 2 drachms six-hourly for seven days (total dosage 7 g.). Eight weeks later he developed whooping cough and was again given chloromycetin palmitate, 2 drachms six-hourly for seven days (total dosage 7 g.). Shortly after the drug was discontinued his parents noticed that he was pale. Five weeks later he developed tonsillitis and was treated with oral penicillin. He gave no history of bleeding into the skin or elsewhere, and, apart from increasing pallor and tiredness, there were no abnormal symptoms.

On admission to hospital the temperature, pulse rate and respiration rate were normal and the only abnormal signs were marked pallor and an apical systolic murmur.

A blood count gave Hb 32% (4·7%), white cell count 7,000 per c.mm. (neutrophils 11%, lymphocytes 89%), platelet count 46,000 per c.mm., reticulocytes less than 1%. Bleeding and clotting times were normal.

Radiographs of the long bones were normal.

Results of sternal marrow puncture were:

Reticulum cells	3·2%
Myeloblasts	0·8%
Promyelocytes	2·0%
Neutrophil myelocytes	4·4%
,, metamyelocytes	10·4%
,, polymorphonuclear cells	7·6%
,, band cells	7·2%
Eosinophil myelocytes	1·2%
,, metamyelocytes	0·8%
,, polymorphonuclear cells	0·4%
Unclassified cells	1·2%
Lymphocytes	40·4%
Mononuclear cells	0·4%
Pronormoblasts	0·4%
Macronormoblasts	0·4%
Basophilic normoblasts	4·0%
Polychromic ,,	10·4%
Orthochromic ,,	4·8%

The marrow smears showed a relatively acellular marrow in which there were very few cells in mitosis. Both leucopoietic and erythropoietic tissue was greatly depressed and the more primitive precursors were scanty. No megakaryocytes could be identified. Many of the erythrocytes showed punctate basophilia.

A diagnosis of hypoplastic anaemia was made and treatment with a number of haematinics was given (Fig. 1). During the period of treatment, lasting 41 weeks, he received ferrous sulphate, 300 mg. daily, and for the first 13 weeks he was given vitamin C, 200 mg. daily. During the initial five weeks of treatment liver extract ('campolon', 2 ml.) was given intramuscularly

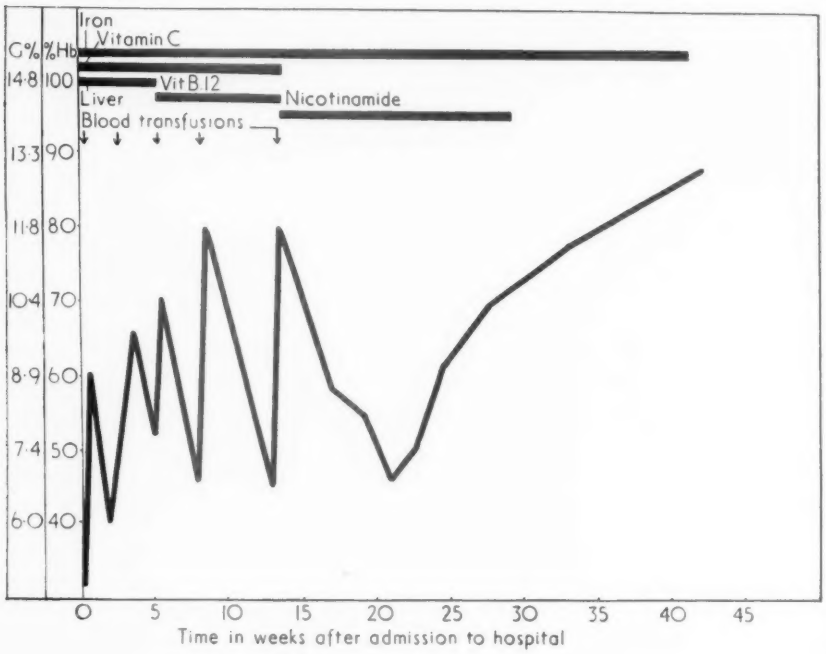

FIG. 1.

twice weekly, and for the next eight weeks he was given vitamin B12, 75 mg. daily by mouth. From the thirteenth week to the thirty-sixth week he received 50 mg. of nicotinamide daily by mouth and in addition he was given an intravenous injection of 100 mg. nicotinamide during the thirteenth week. Transfusions of whole blood or packed red cells were given on five occasions during the first three months of treatment. During this period further bone marrow studies were performed and no alteration in the marrow picture was found. The rate of fall of haemoglobin was steady during this period but shortly after nicotinamide was started a reticulocytosis of over 2% was present in the peripheral blood, whereas previously the reticulocyte count had been less than 1%, and a further bone marrow puncture showed evidence of regeneration. The level of haemoglobin, however, continued to fall but, because of the evidence of blood regeneration revealed by the reticulocyte count and bone marrow studies, no further transfusions were given and subsequently the haemoglobin rose steadily and the boy recovered completely. Throughout the early stages of treatment the platelet count varied from 29,000 to 55,000 per c.mm.; it was 73,000 per c.mm. at the twenty-seventh week and 126,000 per c.mm. at the thirty-third week. No haemorrhages occurred into the skin, alimentary tract, or urinary tract.

Discussion

Many substances have been prescribed for patients suffering from anaemias of the hypoplastic or aplastic type. They have included copper, cobalt, manganese, folic acid, thyroxin, insulin, testosterone, stilboestrol, vitamin C, vitamin B12, A.C.T.H. and cortisone. Boon and Walton (1951) concluded from their experience of 25 patients that no drug had yet proved of value and that blood transfusion was the mainstay of treatment. Adams (1951) described 27 cases of aplastic anaemia and came to the same conclusion. Transfusion seemed to prolong life and one of his patients received 217 pints of blood over a period of nine years.

There is experimental evidence that in rabbits (Vasile, 1940) and in dogs (Handler and Featherston, 1943) nicotinamide plays a part in the maturation of red blood cells but there is no direct evidence that this substance is essential for normal erythropoiesis in human beings. Nicotinamide, which is the amide of nicotinic acid and has the advantage of not causing vasodilatation, is thought to act as a coenzyme, and lack of this vitamin results in interference with respiration of the immature red cells. Normal red blood cells contain relatively large amounts of nicotinic acid (Bicknell and Prescott, 1946).

In this patient, recovery from the hypoplastic anaemia began shortly after nicotinamide was started. This response may have been entirely fortuitous and may have coincided with spontaneous regeneration of the bone marrow; or it may have resulted from delayed action of one of the other haematinics which had been prescribed; or nicotinamide may have exerted a beneficial effect on red cell production. Whatever the explanation it would seem to be reasonable to give nicotinamide to patients suffering from this form of anaemia, especially since no other treatment apart from blood transfusion is known to have a beneficial effect on the course of the disease. Many of the fatal cases

that have been reported died from haemorrhage which was uncontrollable in spite of blood transfusions, but this patient was fortunate in that he did not have any bleeding episodes.

Summary

The clinical findings in a boy of 6 years of age suffering from hypoplastic anaemia after chloramphenicol are reported. The details of treatment are described and it is thought that nicotinamide may have had a beneficial effect on the anaemia.

I am indebted to Dr. B. G. Ockenden for the bone marrow studies and to Professor Norman B. Capon for his advice.

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BOOK REVIEWS

A Thousand Families in Newcastle upon Tyne. By JAMES SPENCE, W. S. WALTON, F. J. W. MILLER and S. D. M. COURT. (Pp. 217; illustrated; 10s. 6d.)*

Many people have been eagerly awaiting this book. Its easy reading, absorbing interest, novel ideas and robust opinions leave us in no doubt that the hand and mind of Spence has written, and tragically moved on. His friends and colleagues in Newcastle have seen to it that the essential and urgent needs encompassed in an advancing world of paediatrics are appropriately discussed and summarized around the factual evidence of the health and illness of the children in the first year of life in the thousand families studied.

Every aspect of the impact of environment, both domiciliary and hospital, is considered in relation to type of illness, length and severity of illness, and consequential matters. Prejudice and bias are singularly lacking, so that there is nothing in the book that is not, in one way or another, quite important. Many paediatricians and health workers must have had similar though perhaps more fugitive ideas, but here, for the first time, these notions and suggestions are clearly in print for all to see and to absorb.

Child health is an expanding subject; there are no limiting factors, because each and every day has an effect for good, or not so good, on the rising generation. The home, the school, and the street are involved in these affairs of physical and mental health and not least in the early years. The reasons for the more recent improvements in child health are critically considered, and a correct weight is given to a widening public awareness of better housing, educational aspects of good work in the infant welfare services, and particularly care and common sense inherent in the mothers who listen attentively to good sound advice, in plain English, when it is given by really well informed medical practitioners or social workers.

Special mention is made of improved university teaching on the wider aspects of health and disease in early life, but that much is yet to be done to bring home the real and effective factors in prevention. A more realistic education for undergraduates and graduates is advocated.

This book is really a global study of medicine as it should be taught and practised. The family doctor will quickly appreciate that his place in the medical hierarchy should be second to none, but it will be all the more effective by building up on the ideas so clearly stated by Spence and his colleagues, not least in realizing the urgent need to work with and for the real family and public health.

Much of the present fragmentation of medical effort could and should be gathered up, so that in each local area of appropriate size all the clinical and administrative services should be well aware of what each is doing. Nowadays, excessive overlap or duplication is too expensive. The factors toward health can be economically encouraged, but only by team work and a real understanding of the fundamental factors concerned.

The story contained in *A Thousand Families* illuminates all this, in revealing the past in vivid contrast to the present, and for sound guidance of us all in the future. It was a happy thought to include the group photograph in which the late Sir James Spence is seen as the vivid mentor of the energetic team responsible for this record of domiciliary research.

* Published for the Nuffield Foundation and the Nuffield Provincial Hospital Trust by Geoffrey Cumberlege (Oxford University Press, 1954).

Modern Problems in Paediatrics. Edited by A. HOTTINGER and F. HAUSER. (Pp. 816; illustrated. Sw.frs. 60.-) Basle: S. Karger.

This interesting volume has been produced as a tribute by his colleagues and friends to Professor Freudenberg on his 70th birthday. Professor Freudenberg came to Basle from Marburg in Germany in 1938 and has 141 publications to his name, mainly on subjects related to the physiological chemistry of infants. The book is a remarkable tribute to 'a scientist who throughout his life has worked for the synthesis of laboratory, clinic and practice'.

The contributors to this 800-page book number over 120 and are drawn from Europe, where Swiss writers naturally predominate, and the U.S.A. Professor McCance and Dr. Widdowson are the only British contributors with an article on 'The Effect of Birth on Renal Function'. All the articles are short and written in either German, French or English with translated summaries. Each author writes on a subject in which he is an expert and the book covers most of the field of topical and current paediatrics. Many of the articles are illustrated. It is proposed to publish further volumes under the same title in due course.

Amongst the distinguished list of contributors may be cited Clement Smith on 'Perinatal Mortality', Lelong and Le Tan Vinh on 'Pneumcystis', Wilkins *et al.* on 'Treatment of Virilising Adrenal Hyperplasia', Fanconi on 'Neuroallergie', Debré on 'La Maladie des Griffes de Chat', Wallgren on 'Complications of Primary Tuberculosis' and van Creveld on 'Recent Advances in Haemorrhagic Disorders'.

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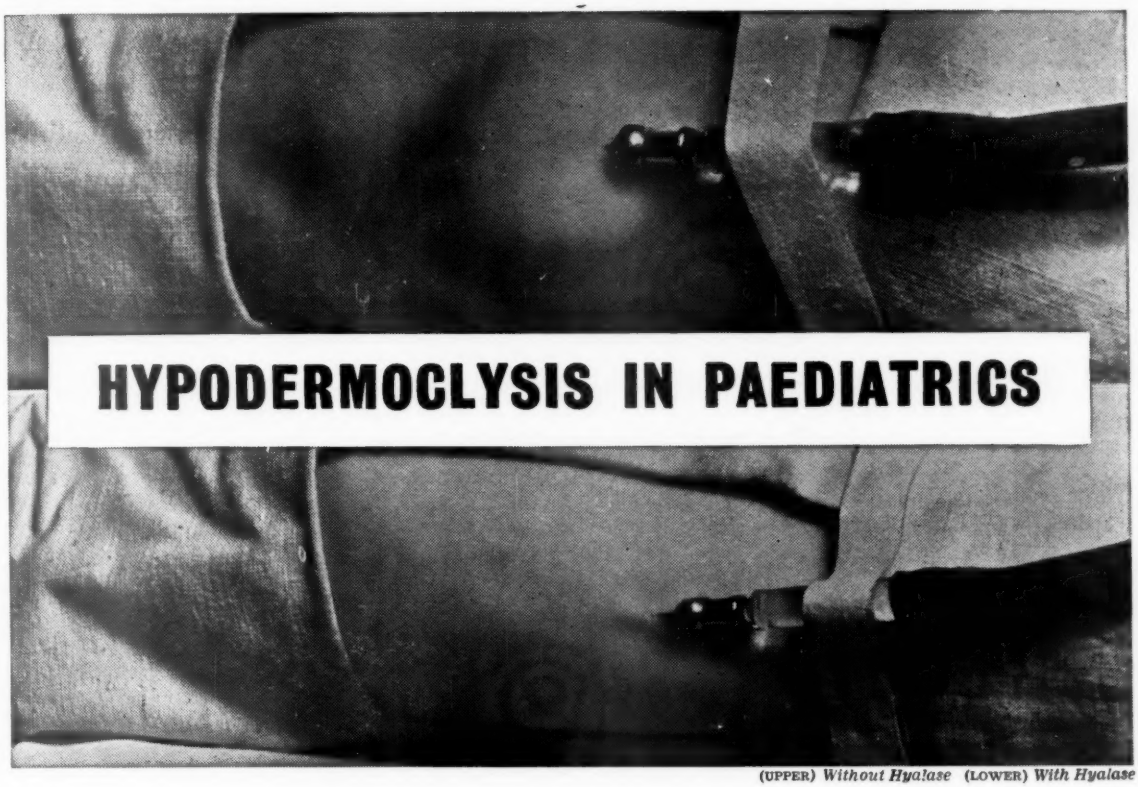

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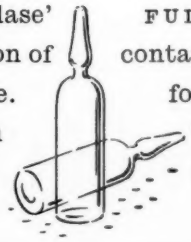

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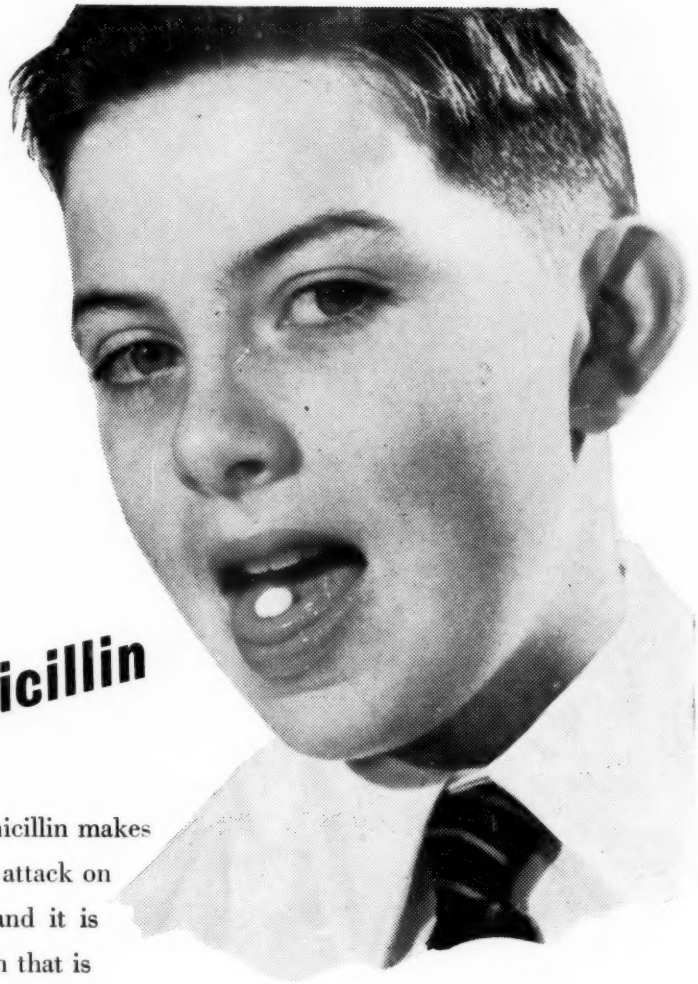

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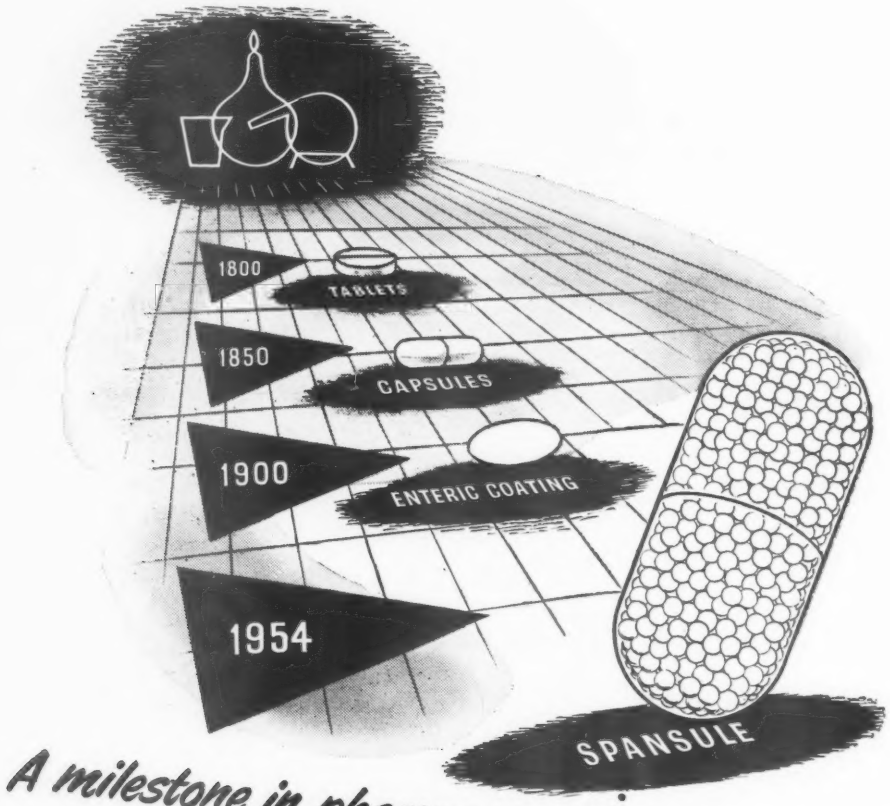

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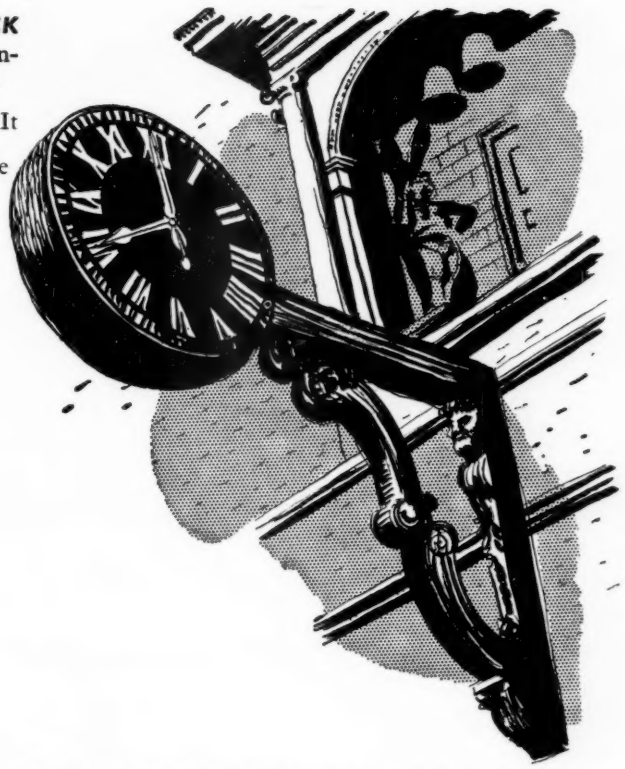

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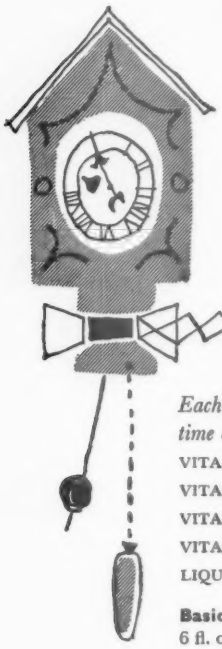

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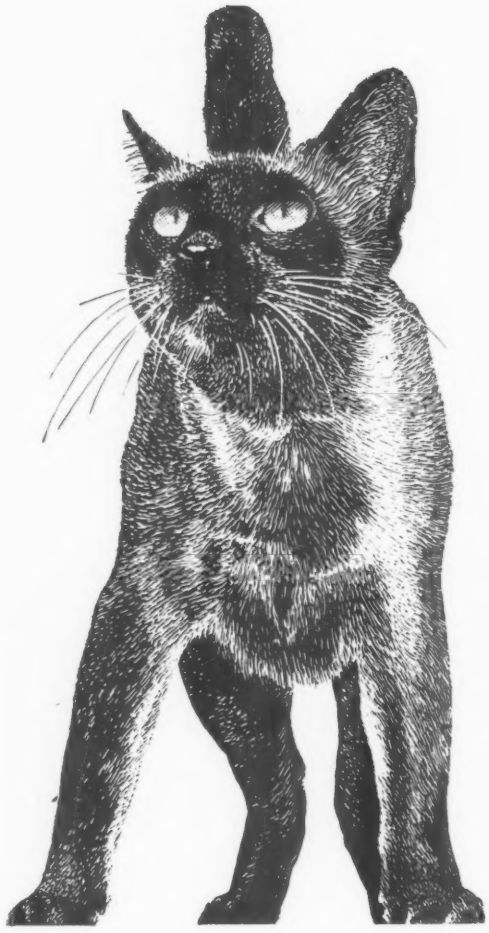

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